

**U.S. HIGH PRODUCTION VOLUME (HPV)  
CHEMICAL CHALLENGE PROGRAM**

**ROBUST SUMMARIES**

**for**

**ACETIC ACID AND SALTS CATEGORY**

**Prepared by  
American Chemistry Council  
Acetic Acid and Salts Panel**


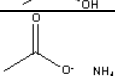

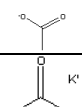
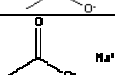
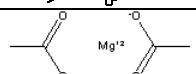


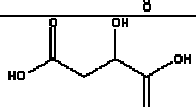
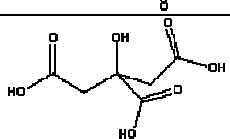
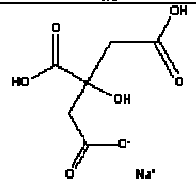
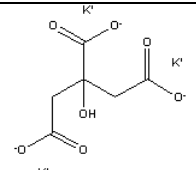
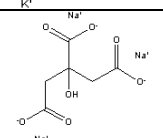
**June 28, 2001**

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## 1. GENERAL SUBSTANCE INFORMATION

Robust summaries for the following substances are included in this Acetic Acid and Salts Category.

Chemical	CAS #	Structure
Acetic Acid	64-19-7	
Acetic Acid, Ammonium Salt	631-61-8	
Acetic Acid, Calcium Salt	62-54-4	
Acetic Acid, Potassium Salt	127-08-2	
Acetic Acid, Sodium Salt	127-09-3	
Acetic Acid, Magnesium Salt	142-72-3	
Acetic Acid, Manganese Salt	638-38-0	
Fumaric Acid	110-17-8	
Malic Acid	6915-15-7	
Citric Acid	77-92-9	
Citric Acid, Sodium Salt	994-36-5	
Citric Acid, Tripotassium Salt	866-84-2	
Citric Acid, Trisodium Salt	68-04-2	

## 2. PHYSICAL-CHEMICAL DATA

### 2.1 MELTING POINT

(a)

Value: 16.7 °C  
Decomposition: Yes ☐ No ☐ Ambiguous ☒  
Sublimation: Yes ☐ No ☐ Ambiguous ☒  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Acetic Acid (64-19-7)  
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value: 114 °C  
Decomposition: Yes ☐ No ☐ Ambiguous ☒  
Sublimation: Yes ☐ No ☐ Ambiguous ☒  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(c)

Value: 80 °C  
Decomposition: Yes ☐ No ☐ Ambiguous ☒  
Sublimation: Yes ☐ No ☐ Ambiguous ☒  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Acetic Acid, Magnesium Salt (142-72-3)  
References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed. Whitehouse Station: Merck Research Laboratories.

(d)

Value: 292 °C  
Decomposition: Yes ☐ No ☐ Ambiguous ☒  
Sublimation: Yes ☐ No ☐ Ambiguous ☒

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid, Potassium Salt (127-08-2)

References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)

Value: 58 °C

Decomposition: Yes ☐ No ☐ Ambiguous ☒ [X]

Sublimation: Yes ☐ No ☐ Ambiguous ☒ [X]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)

Value: 287 °C

Decomposition: Yes ☐ No ☐ Ambiguous ☒ [X]

Sublimation: Yes ☐ No ☐ Ambiguous ☒ [X]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Fumaric Acid (110-17-8)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)

Value: 128 °C

Decomposition: Yes ☐ No ☐ Ambiguous ☒ [X]

Sublimation: Yes ☐ No ☐ Ambiguous ☒ [X]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Malic Acid (6915-15-7)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)

Value: 153 °C

Decomposition: Yes ☐ No ☐ Ambiguous ☒

Sublimation: Yes ☐ No ☐ Ambiguous ☒

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Citric Acid (77-92-9)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)

Value: 211 °C

Decomposition: Yes ☐ No ☒ Ambiguous ☐

Sublimation: Yes ☐ No ☒ Ambiguous ☐

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid, Tripotassium Salt (866-84-2)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)

Value: 150 °C

Decomposition: Yes ☒ No ☐ Ambiguous ☐

Sublimation: Yes ☐ No ☒ Ambiguous ☐

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
OECD Guideline 102

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid, Trisodium Salt (64-08-2)

Remarks: Decomposition begins at 150°C with water loss.

References: European Commission. 1996. Trisodium Citrate. International Uniform Chemical Information Database.

## 2.2 BOILING POINT

(a)

Value: 118.1 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid (64-19-7)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value: 160 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Remarks: Substance decomposes above the reported value.

Test substance: Acetic Acid, Calcium Salt (62-54-4)

References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed. Whitehouse Station: Merck Research Laboratories.

(c)

Value: > 400 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Remarks: Substance decomposes above the reported value.

Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.

(d)

Value: 290 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Remarks: Sublimes.

Test substance: Fumaric Acid (110-17-8)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)

Value: 140 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Remarks: Substance decomposes above the reported value.

Test substance: Malic Acid ( 6915-15-7)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(f)

Value: Decomposes

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Citric Acid (77-92-9)

References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)

Value: 230 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Remarks: Substance decomposes when heated to the reported value.

Test substance: Citric Acid, Tripotassium Salt (866-84-2)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(h)

Value: Decomposes at red heat.

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Citric Acid, Trisodium Salt (64-08-2)

References: Lewis, R.J., Sr. 1994. Hawley's Condensed Chemical Dictionary. 12<sup>th</sup> Ed. New York: Van Nostrand Reinhold Co.

## 2.4 VAPOUR PRESSURE

(a)

Value: 15.2 hPa (11.4 mm Hg)

Temperature: 20 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid (64-19-7)



References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value:  $1.9 \times 10^{-4}$  hPa ( $1.4 \times 10^{-4}$  mm Hg)

Temperature: 25 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Calculated [X]; measured [ ]

GLP: Yes [ ] No [X] ? [ ]

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)

Value: 19.6 hPa (14.7 mm Hg)

Temperature: 25 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Calculated [X]; measured [ ]

GLP: Yes [ ] No [X] ? [ ]

Test substance: Acetic Acid, Calcium Salt (62-54-4)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)

Value:  $9.44 \times 10^{-7}$  hPa ( $7.08 \times 10^{-7}$  mm Hg)

Temperature: 25 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Calculated [X]; measured [ ]

GLP: Yes [ ] No [X] ? [ ]

Test substance: Acetic Acid, Potassium Salt (127-08-2)

References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)

Value:  $9.44 \times 10^{-7}$  hPa ( $7.08 \times 10^{-7}$  mm Hg)

Temperature: 25 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*

Calculated [X]; measured [ ]

GLP: Yes [ ] No [X] ? [ ]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Syracuse Research Corporation Estimation Software.  
EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)  
Value:  $2.05 \times 10^{-4}$  hPa ( $1.54 \times 10^{-4}$  mm Hg)  
Temperature: 25 °C  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Fumaric Acid (110-17-8)  
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)  
Value:  $6.1 \times 10^{-6}$  hPa ( $4.6 \times 10^{-6}$  mm Hg)  
Temperature: 25 °C  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated ☒; measured ☐  
GLP: Yes ☐ No ☒ ? ☐  
Test substance: Malic Acid (6915-15-7)  
References: Syracuse Research Corporation Estimation Software.  
EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(h)  
Value:  $4.9 \times 10^{-9}$  hPa ( $3.7 \times 10^{-9}$  mm Hg)  
Temperature: 25 °C  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated ☒; measured ☐  
GLP: Yes ☐ No ☒ ? ☐  
Test substance: Citric Acid (77-92-9)  
References: Syracuse Research Corporation Estimation Software.  
EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(i)  
Value:  $2.79 \times 10^{-12}$  hPa ( $2.09 \times 10^{-12}$  mm Hg)  
Temperature: 25 °C  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated ☒; measured ☐  
GLP: Yes ☐ No ☒ ? ☐  
Test substance: Citric Acid, Tripotassium Salt (866-84-2)  
References: Syracuse Research Corporation Estimation Software.  
EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)  
 Value: 2.79 x 10<sup>-12</sup> hPa (2.09 x 10<sup>-12</sup> mm Hg)  
 Temperature: 25 °C  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Calculated [X]; measured [ ]  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Citric Acid, Trisodium Salt (64-08-2)  
 References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

## 2.5 PARTITION COEFFICIENT logK<sub>ow</sub>

(a)  
 Log Kow: -0.17  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid (64-19-7)  
 References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)  
 Log Kow: -2.79  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Calculated [X]; measured [ ]  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
 References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(c)  
 Log Kow: -0.97  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Calculated [X]; measured [ ]  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Calcium Salt (62-54-4)  
 References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(d)  
Log Kow: -3.72  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated [X]; measured [ ]  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: Acetic Acid, Potassium Salt (127-08-2)  
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(e)  
Log Kow: -3.72  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Calculated [X]; measured [ ]  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: Acetic Acid, Sodium Salt (127-09-3)  
References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(f)  
Log Kow: 0.33  
Temperature: 23 °C  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Fumaric Acid (110-17-8)  
References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(g)  
Log Kow: -1.26  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Malic Acid (6915-15-7)  
References: Hansch, C. and Leo, A. 1987. The Log P Database. Claremont, CA: Pomona College. In Hazardous Substances Databank (HSDB). Malic Acid. 1999. National Library of Medicine, Bethesda, MD.

(h)  
Log Kow: -1.72  
Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]  
 Test substance: Citric Acid (77-92-9)  
 References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(i)  
 Log Kow: -0.28  
 Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
 Calculated ☒ [X]; measured ☐ [ ]

GLP: Yes ☐ No ☒ [X] ? ☐ [ ]  
 Test substance: Citric Acid, Tripotassium Salt (866-84-2)  
 References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

(j)  
 Log Kow: -0.28  
 Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
 Calculated ☒ [X]; measured ☐ [ ]

GLP: Yes ☐ No ☒ [X] ? ☐ [ ]  
 Test substance: Citric Acid, Trisodium Salt (64-08-2)  
 References: Syracuse Research Corporation Estimation Software. EPIWIN V.2.2. 1993-1997. Syracuse Research Corporation.

## 2.6 WATER SOLUBILITY

### A. Solubility

(a)  
 Value: 50 g/L  
 Temperature: 20 °C  
 Description: Miscible ☐ [ ]; Of very high solubility ☐ [ ];  
 Of high solubility ☐ [ ]; Soluble ☒ [X]; Slightly soluble ☐ [ ]  
 Of low solubility ☐ [ ]; Of very low solubility ☐ [ ]; Not soluble ☐ [ ]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
 Not stated

GLP: Yes ☐ No ☐ [ ] ? ☒ [X]  
 Test substance: Acetic Acid (64-19-7)  
 References: Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Value: 1,480 g/L

Temperature: 4 °C

Description: Miscible [ ]; Of very high solubility [X];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

References: Lide, D.R. (ed). 1999. CRC Handbook of Chemistry  
and Physics. 80<sup>th</sup> Ed. Boca Raton: CRC Press.

(c)

Value: 430 g/L

Temperature: 25 °C

Description: Miscible [ ]; Of very high solubility [X];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Calcium Salt (62-54-4)

References: Verdugt, B.V. 1992. Calcium acetate. Material Safety  
Data Sheet. In European Commission. 1996. Calcium  
Acetate. International Uniform Chemical Information  
Database.

(d)

Value: Very soluble in water or alcohol

Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [X]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Magnesium Salt (142-72-3)

References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed.  
Whitehouse Station: Merck Research Laboratories.

(e)

Value: Soluble in water or alcohol

Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Manganese Salt (638-38-0)

References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed.  
Whitehouse Station: Merck Research Laboratories.

(f)

Value: 2,530 g/L

Description: Miscible [X]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Potassium Salt (127-08-2)

References: Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of  
Industrial Materials. Eighth Edition. New York: Van  
Nostrand Reinhold Company.

(g)

Value: 365 g/L

Temperature: 20 °C

Description: Miscible [ ]; Of very high solubility [X];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: *[e.g. OECD, other (with the year of publication or  
updated of the method used)]*  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

References: Hoechst, A.G. 1993. Sicherheitsdatenblatt  
Natriumacetat entwaessert (04.03.1993). In European  
Commission. 1996. Sodium Acetate. International  
Uniform Chemical Information Database.

(h)

Value: 7 g/L

Temperature: 25 °C

Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Fumaric Acid (110-17-8)

References: Verschueren, K. 1996. Handbook of Environmental  
Data and Organic Chemicals. New York: John Wiley &  
Sons, Inc.

(i)

Value: 592 g/L

Temperature: 25 °C

Description: Miscible [ ]; Of very high solubility [X];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Malic Acid (6915-15-7)

References: Yalkowsky, S.H. 1989. Arizona Database of Aqueous  
Solubilities. University of Arizona, College of  
Pharmacy. In Hazardous Substances Database (HSDB).  
Malic acid. 1999. National Library of Medicine,  
Bethesda, MD.

(j)

Value: 1,330 g/L

Temperature: 20 °C

Description: Miscible [X]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [ ]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid (77-92-9)

References: Verschueren, K. 1996. Handbook of Environmental  
Data and Organic Chemicals. New York: John Wiley &  
Sons, Inc.

(k)

Value: 63 g/L



Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Calculated

GLP: Yes [ ] No [X] ? [ ]

Test substance: Citric Acid, Tripotassium Salt (866-84-2)

References: Syracuse Research Corporation Estimation Software.  
EPIWIN V.2.2. 1993-1997. Syracuse Research  
Corporation.

(l)

Value: ~425 g/L

Temperature: 25 °C

Description: Miscible [ ]; Of very high solubility [ ];  
Of high solubility [ ]; Soluble [X]; Slightly soluble [ ]  
Of low solubility [ ]; Of very low solubility [ ]; Not  
soluble [ ]

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid, Trisodium Salt (64-08-2)

References: European Commission. 1996. Trisodium Citrate.  
International Uniform Chemical Information Database.

## B. pH Value, pKa Value

(a)

pH Value: 2.5

Concentration: 50 g/L aqueous solution

Temperature: 20 °C

Method: [e.g. OECD, other (with the year of publication or  
updated of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]  
(Where applicable, enter values for the dissociation  
constant(s) and the conditions under which they were  
measured.)

pKa value 4.76 at 25°C

Test substance: Acetic Acid (64-19-7)

References: Hoescht, A.G. 1994. Produktinformation Essigsäure  
der Abt. Marketing Chemikalien (04.03.1994) and  
Sicherheitsdatenblatt Essigsäure, reinst (18.04.1994). In  
European Commission. 1996. Acetic Acid.  
International Uniform Chemical Information Database.  
Serjeant, E.P. and Dempsey, B. 1979. Ionisation  
constants of organic acids in aqueous solution. IUPAC  
Chem. Data Ser. No. 23. In Hazardous Substances

Database (HSDB). 1999. Acetic Acid. National Library of Medicine, Bethesda, MD.

(b)

pH Value: 7.0  
Concentration: 390 g/L (5 M aqueous solution)  
Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured).  
Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed. Whitehouse Station: Merck Research Laboratories.

(c)

pH Value: 7.6  
Concentration: 32 g/L (0.2 M aqueous solution)  
Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)  
Test substance: Acetic Acid, Calcium Salt (62-54-4)  
References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed. Whitehouse Station: Merck Research Laboratories.

(d)

pH Value: 9.7  
Concentration: 98 g/L (1 M aqueous solution)  
Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)  
Test substance: Acetic Acid, Potassium Salt (127-08-2)  
References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed. Whitehouse Station: Merck Research Laboratories.

(e)

pH Value: 7.5-9.0  
Concentration: 50 g/L aqueous solution  
Temperature: 20 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒  
*(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)*

Test substance: Acetic acid, sodium salt (127-09-3)

References: Hoechst, A.G. 1993. Sicherheitsdatenblatt Natriumacetat entwaessert (04.03.1993). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

pH Value: 2.1

Concentration: 5 g/L aqueous solution

Temperature: 20 °C

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒  
*(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)*

pK1 value: 3.02 at 18°C

pK2: 4.46 at 18°C

Test substance: Fumaric Acid (110-17-8)

References: Weast, R.C. (ed.). 1989. Handbook of Chemistry and Physics. 69<sup>th</sup> Ed. Boca Raton: CRC Press. In Hazardous Substances Database (HSDB). 1999. Fumaric acid. National Library of Medicine, Bethesda, MD.

(g)

pK1 value: 3.40

pK2 value: 5.05

GLP: Yes ☐ No ☐ ? ☒

Test substance: Malic Acid (6915-15-7)

References: Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4<sup>th</sup> Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(h)

pH Value: 2.2

Concentration: 0.1 N aqueous solution

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]  
*(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)*

pK1 value: 3.13  
 pK2 value: 4.76  
 pK3 value: 6.40  
 Test substance: Citric Acid (77-92-9)  
 References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed.  
 Whitehouse Station: Merck Research Laboratories.

(i)  
 pH Value: ~8  
 Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
 Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]  
*(Where applicable, enter values for the dissociation constant(s) and the conditions under which they were measured.)*

Test substance: Citric Acid, Trisodium Salt (64-08-2)  
 References: Budavari, S. (ed.). 1996. Merck Index. 12<sup>th</sup> ed.  
 Whitehouse Station: Merck Research Laboratories.

### 3. ENVIRONMENTAL FATE AND PATHWAYS

#### 3.1 STABILITY

##### 3.1.1 PHOTODEGRADATION

(a)  
 Type: Air ☒; Water ☐; Soil ☐; Other ☐  
 Light source: Sunlight ☐; Xenon lamp ☐; Other ☐ Not stated  
 Indirect photolysis:  
   Type of sensitizer: OH  
   Concentration of sensitizer: 1,500,000 molecule/cm<sup>3</sup>  
   Rate constant (radical): 5.1 x 10<sup>-13</sup> cm<sup>3</sup>/molecule\*sec  
   Degradation: ~50% after 21 days  
 Method: calculated ☒; measured ☐  
*[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Calculated by AOPWIN, Version 1.55, April 1994,  
 Syracuse Research

GLP: Yes ☐ No ☒ ? ☐ [X]  
 Test substance: Acetic Acid (64-19-7)  
 Reliability: Klimisch category 2

References: Hoechst, A.G. 1994. Internal calculation. UCV (5.05.94). In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: Air ☐; Water ☐; Soil ☐; Other ☒ Sorbed to silica gel

Light source: Sunlight ☐; Xenon lamp ☒; Other ☐

Light spectrum: 290 nm

Spectrum of substance: *[e.g. lambda (max.) (>295 nm) and epsilon (max.) or epsilon (295nm)]*  
>290 nm

Concentration of substance: Not stated

Direct photolysis:

Degradation: 6.6 % of applied amount after 17 hour exposure

Method: calculated ☐; measured ☒  
*[e.g. OECD, other(with the year of publication or updating of the method used)]*  
The test material was sorbed on silica gel and irradiated with light at 290 nm.

GLP: Yes ☐ No ☒ ?☐

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: Freitag, D., Ballhorn, L. Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of the behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(c)

Type: Air ☒; Water ☐; Soil ☐; Other ☐

Light source: Sunlight ☐; Xenon lamp ☐; Other ☐ Not stated

Relative intensity: Not stated

Indirect photolysis:

Type of sensitizer: OH

Concentration of sensitizer: 500,000 molecule/cm<sup>3</sup>

Rate constant (radical):  $5.3 \times 10^{-12}$  cm<sup>3</sup>/molecule\*sec

Degradation: 50% after 7.3 hours

Method: calculated ☒; measured ☐  
*[e.g. OECD, other(with the year of publication or updating of the method used)]*  
Not stated

GLP: Yes ☐ No ☒ ?☐

Test substance: Fumaric Acid (110-17-8)

Reliability: Klimisch category 2

References: Atkinson, R. 1987. A structure-activity relationship for the estimation of rate constants for the gas-phase reactions of OH radicals with organic compounds. J. Inter. Chem. Kinet. 19:799-828.

(d)  
 Type: Air [X]; Water [ ]; Soil [ ]; Other [ ]  
 Indirect photolysis:  
   Type of sensitizer: OH  
   Concentration of sensitizer:  $5 \times 10^5$  molecules/cm<sup>3</sup>  
   Rate constant (radical):  $7.76 \times 10^{-12}$  cm<sup>3</sup>/molecule\*sec  
   Degradation: Malic acid will degrade in the vapor phase by reaction with photochemically produced hydroxyl radicals at the stated rate, which corresponds to an atmospheric half-life of about 2 days.  
 Method: [e.g. OECD, other(with the year of publication or updating of the method used)]  
 GLP: Yes [ ] No [ ] ?[X]  
 Test substance: Malic Acid (6915-15-7)  
 Reliability: Klimisch category 2  
 References: Meylan, W.M. and Howard, P.H. 1993. Chemosphere 26:2293-2299. In Hazardous Substances Database (HSDB). 1999. Malic acid. National Library of Medicine, Bethesda, MD.

### 3.1.2 STABILITY IN WATER

(a)  
 Remarks: Acids dissociate in water.  
 Test substance: Acetic Acid (64-19-7)

(b)  
 Remarks: Salts dissociate in water.  
 Test substance: Acetic Acid, Ammonium Salt (631-61-8)

(c)  
 Remarks: Salts dissociate in water.  
 Test substance: Acetic acid, calcium salt (62-54-4)

(d)  
 Remarks: Salts dissociate in water.  
 Test substance: Acetic acid, potassium salt (127-08-2)

(e)  
 Remarks: Salts dissociate in water.  
 Test substance: Acetic acid, sodium salt (127-09-3)

(f)  
 Type: Abiotic (hydrolysis) [ ]; biotic (sediment) [ ]  
 Half life: 1-15 days in various natural waters  
 Method: [e.g. OECD, other(with the year of publication or updating of the method used)]  
   River die-away studies  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Fumaric Acid (110-17-8)

Remarks:	(e.g. CAS number, name and percentage of degradation products) Faster degradation occurred in more polluted waters. The degradation half life in distilled water was 55 days.
Reliability:	Klimisch category 2
References:	Saito, N. and Nagao, M. 1978. Okayama-Ken Kankyo Hoken Senta Nempo 2:274-276. In Hazardous Substances Database (HSDB). Fumaric acid. 1999. National Library of Medicine, Bethesda, MD.
(g)	
Remarks:	When released into natural water, malic acid can be expected to biodegrade readily; as shown by a number of screening tests.
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Fournier, J.C, Hormatallah, A., Collu, T., and Froncek, B. 1992. Labelling of microbial biomass with radioactive substrates as a means to estimate pesticide effects in soil. Sci. Total Environ. 123/124:325-332.
(h)	
Remarks:	Acids dissociate in water.
Test substance:	Citric Acid (77-92-9)
(i)	
Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Sodium Salt (994-36-5)
(j)	
Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Tripotassium Salt (866-84-2)
(k)	
Remarks:	Salts dissociate in water.
Test substance:	Citric Acid, Trisodium Salt (64-08-2)
(l)	
Remarks:	Salts dissociate in water.
Test substance:	Acetic acid, manganese salt (638-38-0)
(m)	
Remarks:	Salts dissociate in water.
Test substance:	Acetic Acid, Magnesium Salt (142-72-3)

### 3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

Type: Level I Fugacity Modeling  
Temperature: 25 °C  
Melting Point: 16.7 °C  
Vapor Pressure: 1520 Pa (11.4 mm Hg)  
Water Solubility: 50,000 g/m<sup>3</sup> (50 g/L)  
Octanol-Water Partition: 0.676  
Reaction Half-Lives: Air: 21 days  
Water: 1 day  
Soil: 1 day  
Sediment: 1 day  
Results: Partitioning to:  
Air: 26.9 %  
Water: 73.1%  
Soil: 0.044%  
Sediment:  $9.72 \times 10^{-4}$  %  
Suspended Sediment:  $3.04 \times 10^{-5}$  %  
Fish:  $2.47 \times 10^{-6}$  %  
Test Substance: Acetic Acid (64-17-9)  
Reliability: Klimisch category 2  
Reference: Mackay 1991

Type: Level I Fugacity Modeling  
Temperature: 25 °C  
Melting Point: 287 °C  
Vapor Pressure: 0.0205 Pa ( $1.54 \times 10^{-4}$  mm Hg)  
Water Solubility: 7,000 g/m<sup>3</sup> (7 g/L)  
Octanol-Water Partition: 2.138  
Reaction Half-Lives: Air: 0.3 days  
Water: 1 day  
Soil: 1 day  
Sediment: 1 day  
Results: Partitioning to:  
Air:  $6.84 \times 10^{-3}$  %  
Water: 99.8%  
Soil: 0.189%  
Sediment:  $4.20 \times 10^{-3}$  %  
Suspended Sediment:  $1.31 \times 10^{-4}$  %  
Fish:  $1.07 \times 10^{-5}$  %  
Test Substance: Fumaric Acid (110-17-8)  
Reliability: Klimisch category 2  
Reference: Mackay 1991



Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	128 °C
Vapor Pressure:	$6.1 \times 10^{-4}$ Pa ( $4.6 \times 10^{-6}$ mm Hg)
Water Solubility:	592,000 g/m <sup>3</sup> (592 g/L)
Octanol-Water Partition:	0.055
Reaction Half-Lives:	Air: 2 days Water: 1 day Soil: 1 day Sediment: 1 day
Results:	Partitioning to: Air: $2.79 \times 10^{-6}$ % Water: 100.0% Soil: $4.87 \times 10^{-3}$ % Sediment: $1.08 \times 10^{-4}$ % Suspended Sediment: $3.38 \times 10^{-6}$ % Fish: $2.75 \times 10^{-7}$ %
Test Substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

Type:	Level I Fugacity Modeling
Temperature:	25 °C
Melting Point:	153 °C
Vapor Pressure:	$4.9 \times 10^{-7}$ Pa ( $3.7 \times 10^{-9}$ mm Hg)
Water Solubility:	$1.33 \times 10^6$ g/m <sup>3</sup> (1330 g/L)
Octanol-Water Partition:	0.019
Reaction Half-Lives:	Water: 1 day Soil: 1 day Sediment: 1 day
Results:	Partitioning to: Air: $1.43 \times 10^{-9}$ % Water: 100.0% Soil: $1.69 \times 10^{-3}$ % Sediment: $3.75 \times 10^{-5}$ % Suspended Sediment: $1.17 \times 10^{-6}$ % Fish: $9.53 \times 10^{-8}$ %
Test Substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2
Reference:	Mackay 1991

### 3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

Remarks:	See biodegradation
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### 3.5 BIODEGRADATION

(a)

Type: Aerobic [ ]; Anaerobic [X]  
 Inoculum: Adapted [ ]; Non-adapted [X];  
 Concentration of the chemical: 30 mg-C/l related to COD [ ]; DOC [X];  
 Test substance [ ]  
 Medium: Water [ ]; Water-sediment [ ]; Soil [ ];  
 Sewage treatment [X]  
 Degradation: 99 % reduction after 7 days  
 Results: Readily biodeg. [X]; Inherently biodeg. [ ]; Under test  
 condition no biodegradation observed [ ]; Other [ ]  
 Method: [e.g. OECD, others(with the year of publication or  
 updating of the method used)]  
 Test procedures were carried out in an enclosed glove  
 box with N<sub>2</sub> atmosphere. Oxygen-free water was used.  
 The test period was 4 weeks at 37 °C and with pH  
 adjusted to 7. Biodegradation was determined by  
 analyzing the decrease of DOC.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic acid (64-17-9)  
 Reliability: Klimisch category 2  
 References: Kameya, T., Murayama, T., Urano, K., and Kitano, M.  
 1995. Biodegradation ranks of priority organic  
 compounds under anaerobic conditions. Sci. Total  
 Environ. 170(1-2):43-51.

(b)

Results: Biodegrades in days to weeks.  
 Method: [e.g. OECD, others(with the year of publication or  
 updating of the method used)]  
 Calculated.  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
 Reliability: Klimisch category 2  
 References: Syracuse Research Corporation Estimation Software.  
 EPIWIN V.2.2. 1993-1997. Syracuse Research  
 Corporation.

(c)

Type: Aerobic [X]; Anaerobic [ ]  
 Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage  
 treatment [X]  
 Results: Readily biodeg. [X]; Inherently biodeg. [ ]; Under test  
 condition no biodegradation observed [ ]; Other [ ]  
 Method: [e.g. OECD, others(with the year of publication or  
 updating of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic acid, calcium salt (62-54-4)

Remarks: Activated sludge, industrial  
 Reliability: Klimisch category 4  
 References: European Commission. 1996. Calcium acetate. International Uniform Chemical Information Database.

(d)  
 Type: Aerobic [X]; Anaerobic [ ]  
 Inoculum: Adapted [ ]; Non-adapted [X]; activated sludge  
 Concentration of the chemical: 160 mg/L related to COD [ ]; DOC [ ];  
 Test substance [X]  
 Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]  
 Degradation: 100 % reduction after 5 days  
 Results: Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]  
 Method: [e.g. OECD, others(with the year of publication or updating of the method used)]  
 OECD Guideline 302B (1981) "Inherent biodegradability: Modified Zahn-Wellens Test"  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Sodium Salt (127-09-3)  
 Reliability: Klimisch category 2  
 References: Huels study (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(e)  
 Type: Aerobic [X]; Anaerobic [ ]  
 Inoculum: Adapted [ ]; Non-adapted [X];  
 Concentration of the chemical: 0.05 mg/L related to COD [ ]; DOC [ ];  
 Test substance [X]  
 Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]  
 Degradation: 52.6 % reduction after 5 days  
 Results: Readily biodeg. [ ]; Inherently biodeg. [X]; Under test condition no biodegradation observed [ ]; Other [ ]  
 Method: [e.g. OECD, others(with the year of publication or updating of the method used)]  
 Batch-Test; mineralization related to maximum theoretical CO<sub>2</sub>-production; measurement of 14 CO<sub>2</sub>;  
 Temperature was maintained at 25 ± 2 °C.  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Sodium Salt (127-09-3)  
 Reliability: Klimisch category 2  
 References: Freitag, D., Ballhorn, L., Geyer, H., and Korte, F. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of the behavior of organic chemicals in the ecosphere by means of simple laboratory tests with C14 labeled chemicals. Chemosphere 14(10):1589-1616.

(f)

Type: Aerobic [X]; Anaerobic [ ]

Inoculum: Adapted [ ]; Non-adapted [X]; predominantly domestic sewage

Concentration of the chemical: 10 mg/L related to COD [ ]; DOC [X]; Test substance [ ]

Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]

Degradation: 98 % reduction after 21 days

Results: Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]

Method: *[e.g. OECD, others(with the year of publication or updating of the method used)]*  
OECD Guideline 301 E (1981) "Ready biodegradability: Modified OECD Screening Test"

GLP: Yes [ ] No [X] ? [ ]

Test substance: Fumaric Acid (110-17-8)

Reliability: Klimisch category 2

References: Huels, A.G. 1992. Unpublished results dated 3/4/92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(g)

Type: Aerobic [X]; Anaerobic [ ]

Inoculum: Adapted [ ]; Non-adapted [X]; domestic sewage

Concentration of the chemical: 600 mg/L related to COD [ ]; DOC [ ]; Test substance [X]

Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage treatment [X]

Degradation: 98 % reduction after 48 hours

Results: Readily biodeg. [X]; Inherently biodeg. [ ]; Under test condition no biodegradation observed [ ]; Other [ ]

Kinetics: 0% in 0 hours  
34% in 18 hours  
84% in 24 hours  
97% in 40 hours  
98% in 48 hours

Method: *[e.g. OECD, others(with the year of publication or updating of the method used)]*  
OECD Guideline 302 B (1994) "Inherent biodegradability: Modified Zahn-Wellens Test"

GLP: Yes [X] No [ ] ? [ ]

Test substance: Citric Acid (77-92-9)

Reliability: Klimisch category 2

References: European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(h)

Type: Aerobic [X]; Anaerobic [ ]

Inoculum: Adapted [ ]; Non-adapted [ ]; effluent from domestic sewage treatment plant

Concentration of the chemical: 5 mg/L related to COD [ ]; DOC [ ];  
 Test substance [X]  
 Medium: Water [ ]; Water-sediment [ ]; Soil [ ]; Sewage  
 treatment [X]  
 Degradation: 90 % reduction after 30 days  
 Results: Readily biodeg. [X]; Inherently biodeg. [ ]; Under test  
 condition no biodegradation observed [ ]; Other [ ]  
 Method: [e.g. OECD, others(with the year of publication or  
 updating of the method used)]  
 GLP: Yes [ ] No [X] ? [ ]  
 Directive 84/449/EEC, C.6 “Biotic degradation – closed  
 bottle test”  
 Test substance: Citric Acid, Trisodium Salt (64-08-2)  
 Reliability: Klimisch category 2  
 References: European Commission. 1996. Trisodium citrate.  
 International Uniform Chemical Information Database.

### 3.7 BIOACCUMULATION

Remarks: Does not bioaccumulate because these acids and their  
 salts dissociate and biodegrade rapidly.

## 4. ECOTOXICITY

### 4.1 ACUTE/PROLONGED TOXICITY TO FISH

(a)  
 Type of test: Static [ ]; Semi-static [ ]; Flow-through [ ]; Other (e.g.  
*field test*) [ ]; Not stated  
 Species: *Lepomis macrochirus* (Bluegill sunfish)  
 Exposure period: 96 hours  
 Results: LC<sub>50</sub> (96 h) = 75 mg/L  
 Analytical monitoring: Yes [ ]; No [ ]; ? [X]  
 Method: [e.g. OECD, other (with the year of publication or  
 updated of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid (64-19-7)  
 Remarks: Data from unknown literature source as cited by Price.  
 Reliability: Klimisch category 2  
 References: Price, K.S., Waggy, G.T., and Conway, R.A. 1974.  
 Brine shrimp bioassay and seawater BOD of  
 petrochemicals. J. Water Pollut Control Fed. 46(1):63-  
 77.

(b)

Type of test: Static ☒; Semi-static ☐; Flow-through ☐; Other (*e.g. field test*) ☐; Not stated

Species: *Gambusia affinis* (Mosquito fish)

Exposure period: 96 hours

Results:  $LC_{50}$  (96 h) = 251 mg/L

Analytical monitoring: Yes ☐; No ☐; ? ☒

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Test water was maintained at pH 6.9 – 8.7 and 16-25°C

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid (64-19-7)

Remarks: Test data from original citation.

Reliability: Klimisch category 2

References: Wallen I.E., Greer, W.C., and Lasater, R. 1957.  
Toxicity to *Gambusia affinis* of certain pure chemicals in turbid waters. Sewage Ind. Wastes 23(6):695-711.

(c)

Type of test: Static ☒; Semi-static ☐; Flow-through ☐; Other (*e.g. field test*) ☐; Not stated

Species: *Pimephales promelas* (Fathead minnow)

Exposure period: 96 hours

Results:  $LC_{50}$  (96 h) = 79-88 mg/L

Analytical monitoring: Yes ☐; No ☐; ? ☒

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Fathead minnows were exposed under static conditions to a series of concentrations of ammonium acetate.

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

Reliability: Klimisch category 2

References: Mattson, V.R., Arthur, J.W., and Walbridge, C.A. 1976.  
Acute toxicity of selected organic compounds to fathead minnows. Ecol. Res. Ser. EPA-600/3-76-097, Environ. Res. Lab., USEPA, Duluth, MN: 12p.

(d)

Type of test: Static ☐; Semi-static ☐; Flow-through ☐; Other (*e.g. field test*) ☐; Not stated

Species: *Gambusia affinis* (Mosquito fish)

Exposure period: 96 hours

Results:  $LC_{50}$  (96 h) = 238 mg/L

Analytical monitoring: Yes ☐; No ☐; ? ☒

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid, Ammonium Salt (631-61-8)

Reliability: Klimisch category 4

References: Jones, H.R. 1971. Environmental control in the organic and petrochemical industries. Noyes Data Corporation. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(e)

Type of test: Static [ ]; Semi-static [X]; Flow-through [ ]; Other (*e.g. field test*) [ ]

Species: *Salmo gairdneri* (Rainbow trout)

Exposure period: 96 hours

Results:  $LC_{50}$  (96 h) = 6,100 mg/L

Analytical monitoring: Yes [ ]; No [X]; ? [ ]

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]

OECD Guideline 203

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic acid, potassium salt (127-08-2)

Remarks: Test used a commercial formulation.

Reliability: Klimisch category 2

References: Huntingdon Research Centre. 1992. Report No. BPC142/911702. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(f)

Type of test: Static [ ]; Semi-static [X]; Flow-through [ ]; Other (*e.g. field test*) [ ]

Species: *Brachydanio rerio* (Zebra fish)

Exposure period: 96 hours

Results:  $LC_{50}$  (96 h) >100 mg/L

Analytical monitoring: Yes [X]; No [ ]; ? [ ]

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]

Directive 92/69/EEC, C.1 (1992)

GLP: Yes [X] No [ ] ? [ ]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Remarks: Concentration refers to waterfree substance. No mortality was observed at the highest concentration tested.

Reliability: Klimisch category 2

References: Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(g)

Type of test: Static [X]; Semi-static [ ]; Flow-through [ ]; Other (*e.g. field test*) [ ]

Species: *Pimephales promelas* (Fathead minnow)

Exposure period: 120 hours

Results:  $LC_{50}$  (96 h) = 13.3 mg/L

Analytical monitoring: Yes [ ]; No [ ]; ? [X]  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Fathead minnow embryos were exposed to increasing concentrations of acetic acid sodium salt for 5 days under static conditions.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid, Sodium Salt (127-09-3)  
 Remarks: 95% confidence intervals were 12.43 and 14.31 mg/L.  
 Reliability: Klimisch category 2  
 References: DeYoung, D.J., Bantle, J.A., Hull, M.A., and Burks, S.L. 1996. Differences in sensitivity to developmental toxicants as seen in *Xenopus* and *Pimephales* embryos. Bull. Environ. Contam. Toxicol. 56:143-150.

(h)  
 Type of test: Static [X]; Semi-static [ ]; Flow-through [ ]; Other (e.g. field test) [ ]  
 Species: *Brachydanio rerio* (Zebra fish)  
 Exposure period: 48 hours  
 Results: LC<sub>50</sub> (48 h) = 245 mg/L  
 Analytical monitoring: Yes [ ]; No [X]; ? [ ]  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 DIN 38412 Part 15  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Fumaric Acid (110-17-8)  
 Reliability: Klimisch category 2  
 References: Huels Ag: AIDA – Grunddatensatz, date of last update 0.4.03.92. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(i)  
 Type of test: Static [X]; Semi-static [ ]; Flow-through [ ]; Other (e.g. field test) [ ]  
 Species: *Lepomis macrochirus* (Bluegill sunfish)  
 Exposure period: 96 hours  
 Results: LC<sub>50</sub> (96 h) = 1,516 mg/L  
 Analytical monitoring: Yes [ ]; No [ ]; ? [X]  
 Method: [e.g. OECD, other (with the year of publication or updated of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid (77-92-9)  
 Reliability: Klimisch category 4  
 References: Schwartz and Davis. 1973. United States Environmental Protection Agency (USEPA). EPA-600/2-74-003. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.



(j)

Type of test: Static ☐ ; Semi-static ☐ ; Flow-through ☐ ; Other (*e.g. field test*) ☐ ; Not stated

Species: *Poecilia reticulata* (Guppy)

Exposure period: 96 hours

Results: LC<sub>50</sub> (96 h) >18,000-32,000 mg/L

Analytical monitoring: Yes ☒ ; No ☐ ; ? ☐

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Citric Acid, Trisodium Salt (64-08-2)

Remarks: The same result was obtained in a study on *Oryzias latipes* (medaka).

Reliability: Klimisch category 4

References: Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

### A. *Daphnia*

(a)

Type of test: Static ☒ ; Semi-static ☐ ; flow-through ☐ ; Other (*e.g. field test*) ☐ ;

Species: *Daphnia magna*

Exposure period: 24 hours

Results: LC<sub>50</sub> = 47 mg/L

Analytical monitoring: Yes ☐ ; No ☐ ; ? ☒

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid (64-19-7)

Remarks: Based on the results reported in Bringmann and Kuhn 1982 (see next summary for reference), this value is likely attributed to the low pH of the system.

Reliability: Klimisch category 2

References: Elkins, H.F., et al. 1956. Sewage Ind. Wastes 28(12): 1475. In Verschueren, K. 1996. Handbook of Environmental Data and Organic Chemicals. New York: John Wiley & Sons, Inc.

(b)

Type of test: Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]

Species: *Daphnia magna*

Exposure period: 24 hours

Results: EC<sub>50</sub> = 6,000 mg/L

Analytical monitoring: Yes [ ]; No [ ]; ? [X]

Method: [e.g. OECD, other (with the year of publication or updated of the method used)]

The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7)

Remarks: The stated result was for test solutions neutralized (pH 8.0) prior to daphnid exposures. For the un-neutralized test, the 24-hour EC<sub>50</sub> was 95 mg/L. The pH of un-neutralized test solutions was not stated.

Reliability: Klimisch category 2

References: Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on *Daphnia magna strauss* tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.

(c)

Type of test: Static [X]; Semi-static [ ]; flow-through [ ]; Other [ ]

Species: *Daphnia magna*

Exposure period: 48 hours

Results: EC<sub>50</sub> = 65 mg/L

Analytical monitoring: Yes [ ]; No [ ]; ? [X]

Method: [e.g. OECD, other (with the year of publication or updated of the method used)]

*Daphnia magna* were exposed to a series of concentrations of acetic acid. The endpoint was immobilization.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7)

Remarks: Test solutions were apparently un-neutralized.

Reliability: Klimisch category 2

References: Janssen, C.R., Espiritu, E.Q., and Persoone, G. 1993. Evaluation of the new "Enzymatic Inhibition" criterion for rapid toxicity testing with *Daphnia magna*. In: Soares, A. and Calow, P. (Eds.), Progress in Standardization of Aquatic Toxicity Tests. Lewis Publishers, New York, pp. 71-81.

(d)

Type of test: Static ☒; Semi-static ☐; flow-through ☐; Other (*e.g. field test*) ☐; Not stated

Species: *Daphnia magna*

Exposure period: 24 hours

Results:  $LC_{50} = 7,170$  mg/L

Analytical monitoring: Yes ☐; No ☐; ? ☒

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Remarks: Was summarized in the Potassium acetate IUCLID Data Sheet but indicated the test substance was acetic acid, sodium salt.

Reliability: Klimisch category 4

References: Bringmann and Kuhn. 1977. Z. Wasser Abwasser Forschung 10(5):161-166. In European Commission. 1996. Potassium acetate. International Uniform Chemical Information Database.

(e)

Type of test: Static ☒; Semi-static ☐; flow-through ☐; Other (*e.g. field test*) ☐; Not stated

Species: *Daphnia magna*

Exposure period: 48 hours

Results:  $EC_{50} > 1,000$  mg/L

Analytical monitoring: Yes ☐; No ☒; ? ☐

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
Directive 84/449/EEC, C.2

GLP: Yes ☒ No ☐ ? ☐

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: Huels. 1993. Report No. FK 1241 (unpublished). In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.

(f)

Type of test: Static ☒; Semi-static ☐; flow-through ☐; Other (*e.g. field test*) ☐

Species: *Daphnia magna*

Exposure period: 48 hours

Results:  $EC_{50} = 212$  mg/L

Analytical monitoring: Yes ☐; No ☒; ? ☐

Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
First instar *Daphnia* (< 24 hrs old) were used for all tests. Method as described in EPA-660/3-75-009.

GLP: Yes ☐ No ☐ ? ☒

Test substance: Fumaric Acid (110-17-8)

Remarks: Endpoint was immobilization.  
 Reliability: Klimisch category 2  
 References: Randall, T.L. and Knopp, P.V. 1980. Detoxification of specific organic substances by wet oxidation. J. Water Pollut. Control Fed. 52(8):2117-2130.  
 United States Environmental Protection Agency (USEPA). 1975. Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians. Ecological Research Series, EPA-660/3-75-009.

(g)  
 Type of test: Static [X]; Semi-static [ ]; flow-through [ ]; Other (*e.g. field test*) [ ]  
 Species: *Daphnia magna*  
 Exposure period: 48 hours  
 Results:  $LC_{50} = 240$  mg/L  
 Analytical monitoring: Yes [ ]; No [X]; ? [ ]  
 Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
 Fifteen daphnids ( $\leq 24$ -hours old, first instar) were exposed to concentrations of 100, 180, 320, 560 and 1,000 mg/L, along with a control group. Test temperature remained constant at 20 °C throughout the study.  
 GLP: Yes [X] No [ ] ? [ ]  
 Test substance: Malic Acid (6915-15-7)  
 Remarks: Mortality and/or surfacing was observed in test concentrations  $\geq 180$  mg/L. Low pH (3.2-4.5) caused by the acidic test material may be considered the primary cause of the observed toxicity.  
 Reliability: Klimisch category 1  
 References: ABC Laboratories. 1989. Acute freshwater invertebrate toxicity study – malic acid. Report # 37763. Prepared for Proctor & Gamble.

(h)  
 Type of test: Static [X]; Semi-static [ ]; flow-through [ ]; Other (*e.g. field test*) [ ]; Not stated  
 Species: *Daphnia magna*  
 Exposure period: 24 hours  
 Results:  $EC_{50} = 1,535$  mg/L  
 Analytical monitoring: Yes [ ]; No [ ]; ? [X]  
 Method: [*e.g. OECD, other (with the year of publication or updated of the method used)*]  
 The stock cultures of test organisms were fed dry algae, but no feeding occurred during the 24-hour exposure. The testing took place in a defined standardized culture medium (artificial fresh water). The endpoint was immobilization.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid (77-92-9)

Reliability:	Klimisch category 2
References:	Bringmann, V. G. and Kuhn, R. 1982. Results of toxic action of water pollutants on <i>Daphnia magna strauss</i> tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1):1-6.
(i)	
Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other (e.g. field test) [ ]; Not stated
Species:	<i>Daphnia magna</i>
Exposure period:	72 hours
Results:	EC <sub>50</sub> = 120 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	[e.g. OECD, other (with the year of publication or updated of the method used)]
	Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Ellis, M.M. 1937. Bull. Bur. Fish 48:365. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.
(j)	
Type of test:	Static [X]; Semi-static [ ]; flow-through [ ]; Other (e.g. field test) [ ]; Not stated
Species:	<i>Daphnia magna</i>
Exposure period:	48 hours
Results:	EC <sub>50</sub> = 5,600 – 10,000 mg/L
Analytical monitoring:	Yes [ ]; No [ ]; ? [X]
Method:	[e.g. OECD, other (with the year of publication or updated of the method used)]
	Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid, Trisodium Salt (64-08-2), purity: 50%
Reliability:	Klimisch category 4
References:	Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

#### 4.3 TOXICITY TO AQUATIC PLANTS, e.g. algae

(a)	
Species:	<i>Scenedesmus quadricauda</i> (algae)
Endpoint:	Biomass [ ]; Growth rate [ ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT ( toxicity threshold ) = 4,000 mg/L

Analytical monitoring:	Yes <input type="checkbox"/> ; No <input type="checkbox"/> ; ? <input checked="" type="checkbox"/>
Method:	<i>[e.g. OECD, other (with the year of publication or updated of the method used)]</i> Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> ? <input type="checkbox"/>
Test substance:	Acetic Acid (64-19-7)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is $\geq 3\%$ below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. <i>Water Res.</i> 14:231-241.
(b)	
Species:	<i>Anacystis nidulans</i> (Cyanobacterium)
Endpoint:	Biomass <input type="checkbox"/> ; Growth rate <input checked="" type="checkbox"/> ; Other <input type="checkbox"/>
Exposure period:	60 hours
Results:	Growth inhibition in photoautotrophic algae at 2,460 mg/L (0.03 mol/L) after 60 hours.
Analytical monitoring:	Yes <input type="checkbox"/> ; No <input type="checkbox"/> ; ? <input checked="" type="checkbox"/>
Method:	<i>[e.g. OECD, other (with the year of publication or updated of the method used)]</i> A static test was conducted at a temperature of 30°C, a pH of 7.6-7.8, and a light intensity of 1,000 ft. candles. Growth rate was determined by measuring optical density of the cultures.
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/>
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	Retardation of growth (i.e., slowed but did not otherwise restrict growth) occurred at 820 and 1,640 mg/L (0.01 and 0.02 mol/L). Inhibition of growth (i.e., prevented growth) occurred at 2,460 and 3,290 mg/L (0.03 and 0.04 mol/L). However, even at the highest concentrations, the cultures remained viable after being transferred to clean culture water.
Reliability:	Klimisch category 2
References:	Hoare, D.S. et al. 1967. <i>J. Gen. Microbiol.</i> 49:351-370. In European Commission. 1996. Sodium Acetate. International Uniform Chemical Information Database.
(c)	
Species:	<i>Scenedesmus subspicatus</i> (Algae)
Endpoint:	Biomass <input type="checkbox"/> ; Growth rate <input checked="" type="checkbox"/> ; Other <input type="checkbox"/>

Exposure period:	72 hours
Results:	EC <sub>10</sub> ( 72 h) = 32 mg/L EC <sub>50</sub> (72 h) = 41 mg/L CE <sub>90</sub> (72 h) = 49 mg/L
Analytical monitoring:	Yes [ <input type="checkbox"/> ]; No [X]; ? [ <input type="checkbox"/> ]
Method:	[e.g. OECD, other (with the year of publication or updated of the method used)] UBA algal growth inhibition test (proposed method February 1984)
GLP:	Yes [ <input type="checkbox"/> ] No [X] ? [ <input type="checkbox"/> ]
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 2
References:	AIDA – Huels AG Report No. AW 1501. 1988. Not published. In European Commission. 1996. Fumaric Acid. International Uniform Chemical Information Database.
(d)	
Species:	<i>Scenedesmus quadricauda</i> (algae)
Endpoint:	Biomass [ <input type="checkbox"/> ]; Growth rate [ <input type="checkbox"/> ]; Other [X](Growth inhibition)
Exposure period:	8 days
Results:	TT ( toxicity threshold ) = 640 mg/L
Analytical monitoring:	Yes [ <input type="checkbox"/> ]; No [ <input type="checkbox"/> ]; ? [X]
Method:	[e.g. OECD, other (with the year of publication or updated of the method used)] Filled culture tubes were maintained at 27 °C and relative humidity of 50%. The concentration of the algal suspension is measured turbidmetrically (while diffused light is screened off) and expressed by the extinction of the primary light of the monochromatic radiation at 578 nm for a layer of 10 mm thickness.
GLP:	Yes [ <input type="checkbox"/> ] No [X] ? [ <input type="checkbox"/> ]
Test substance:	Citric Acid (77-92-9)
Remarks:	Toxicity threshold is defined as the pollutant concentration resulting in a mean extinction value that is $\geq 3\%$ below the mean of the extinction value for the non-toxic dilutions of the test culture.
Reliability:	Klimisch category 2
References:	Bringmann, G. and Kuhn, R. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14:231-241.
(e)	
Species:	<i>Chlorella vulgaris</i>
Endpoint:	Biomass [X]; Growth rate [ <input type="checkbox"/> ]; Other [ <input type="checkbox"/> ]
Exposure period:	96 hours
Results:	EC <sub>50</sub> > 18,000 – 32,000 mg/L
Analytical monitoring:	Yes [X]; No [ <input type="checkbox"/> ]; ? [ <input type="checkbox"/> ]

Method: *[e.g. OECD, other (with the year of publication or updated of the method used)]*  
 OECD Guideline 201 (1982) “Algae, Growth Inhibition Test”

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Citric Acid, Trisodium Salt (64-08-2); purity: 50% solution

Reliability: Klimisch category 2

References: Sloof, W. and Kappers, F.I. 1982. Rijksinstituut voor drinkwatervoorziening (RID) Nr. 82-4. In European Commission. 1996. Trisodium citrate. International Uniform Chemical Information Database.

## 5. **TOXICITY**

### 5.1 **ACUTE TOXICITY**

#### 5.1.1 **ACUTE ORAL TOXICITY**

(a)

Type: LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ [X]; LDL<sub>0</sub> ☐ ; Other ☐ [ ]

Species/strain: Mouse

Value: 4960 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid (64-19-7)

Reliability: Klimisch category 4

References: Woodward, G., Lang, S.R., Nelson, K.W., and Calvery, H.O. 1941. J. Ind. Hyg. Toxicol. 23:78-82. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)

Type: LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ [X]; LDL<sub>0</sub> ☐ ; Other ☐ [ ]

Species/strain: Rat

Value: 4,280 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, calcium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid, Calcium Salt (62-54-4)

Reliability: Klimisch category 2



References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.  
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani,, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(c)  
Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value: 3,250 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Rats were given a single oral dose of 100,000 mg/L (0.100 g/ml) of acetic acid, potassium salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.

GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Potassium Salt (127-08-2)  
Reliability: Klimisch category 2  
References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.  
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

(d)  
Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value: 3,530 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Sodium Salt (127-09-3)  
Reliability: Klimisch category 2  
References: Food and Agriculture Organization of the United Nations, Report Series. 40,127,67. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)  
Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value: 10,700 mg/kg b.w. (male rats)  
9,300 mg/kg b.w. (female rats)

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Rats were given a single oral dose. Range finding toxicity test as described in Smyth et al. 1962.

GLP: Yes ☐ No ☐ ? ☒

Test substance: Fumaric Acid (110-17-8)

Reliability: Klimisch category 2

References: Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol. Appl. Pharmacol.* 42:417-423.  
 Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. A range-finding toxicity data: List VI. *Amer. Ind. Hyg. Assoc. J.* 23:95-207.

(f)

Type: LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Rat

Value: 10,000 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Fumaric Acid (110-17-8)

Reliability: Klimisch category 4

References: Ullmann's Encyclopedia of Industrial Chemistry. 5<sup>th</sup> Ed. Volume A16. In European Commission. 1996.  
 Fumaric acid. International Uniform Chemical Information Database.

(g)

Type: LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Mouse, Rat

Value: 1,600 – 3,200 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Malic Acid (6915-15-7)

Reliability: Klimisch category 2

References: Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(h)

Type: LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Rat (Sprague-Dawley)

Value: 11,700 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid (77-92-9), purity: 99.8% citric acid monohydrate

Remarks: Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.

Reliability: Klimisch category 2

References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(i)

Type: LD<sub>0</sub> ☐; LD<sub>100</sub> ☐; LD<sub>50</sub> ☒; LDL<sub>0</sub> ☐; Other ☐

Species/strain: Mouse (1 CR)

Value: 5,790 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 0.5 ml/10 g b.w. Behavior and mortality were observed for 7 days.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid (77-92-9), purity : 99.8% citric acid monohydrate

Remarks: Observed effects at the higher concentration included motor ataxia, decreases in respiration and heart beat, and respiratory failure.

Reliability: Klimisch category 2

References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. Lab. 30(1):25-31.

(j)

Type: LD<sub>0</sub> ☐; LD<sub>100</sub> ☐; LD<sub>50</sub> ☒; LDL<sub>0</sub> ☐; Other ☐

Species/strain: Mouse

Value: 7,100 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Citric Acid, Sodium Salt (994-36-5)

Reliability: Klimisch category 4  
References: Oelkers, H.A. 1965. Theor. Med. 19:625. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(k)  
Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat (Wistar)  
Value: 8,610 mg/kg b.w.  
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
A group of 30 albino male and female rats (five per dose) were given either 1.0, 2.0, 4.0, 8.0, 16.0 or 32.0 g/kg bw of acetic acid, magnesium salt in propylene glycol via intubation.  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: Acetic Acid, Magnesium Salt (142-72-3)  
Remarks: No toxic effects were noted at the 1.0 and 2.0 g/kg doses. Diarrhea and ruffled unkempt coats were evident 24-36 hours after intubation at the 4.0 g/kg dose. Deaths in the 16.0 and 32.0 g/kg doses occurred 8-16 hours and within 6 hours, respectively.

Reliability: Klimisch category 2  
References: Green, L.A. 1977. Toxicity Studies for The Shepherd Chemical Company: Acute Oral LD<sub>50</sub> Toxicity Study: Magnesium Acetate. Bio-Toxicology Laboratories, May 31, 1977.

(l)  
Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Value: 3,730 mg/kg b.w.  
Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Rats were given a single oral dose of 200,000 mg/L (0.200 g/ml) of acetic acid, manganese salt in water via intubation. A range-finding toxicity test was conducted as described in Smyth et al. 1962.  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Manganese Salt (638-38-0)  
Reliability: Klimisch category 2  
References: Smyth, H.F., Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Striegel, J.A., and Nycum, J.S. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.  
Smyth, H.F. Jr., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. Amer. Ind. Hyg. Assoc. J. 23:95-207.

### 5.1.2 ACUTE INHALATION TOXICITY

(a)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [X]; LCL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Exposure period: 4 hours  
Value: 11.4 mg/l  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
BASF-Test Protocol  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: Acetic Acid (64-19-7); purity: 96%  
Reliability: Klimisch category 2  
References: BASF, A.G. 1989. Unpublished study No. 78/650, 21.05.1980. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [X]; LCL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Mouse  
Exposure period: 1 hour  
Value: 5,620 ppm  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid (64-19-7)  
Remarks: Inhalation of > 1,000 ppm produced irritation of the conjunctiva and upper respiratory tract.  
Reliability: Klimisch category 4  
References: Ghiringhelli, L. and Difabio, A. 1957. Med. Lav. 48: 559. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(c)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [X]; LCL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Exposure period: 1 hour  
Value: >30 g/m<sup>3</sup>  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Sodium Salt (127-09-3)  
Reliability: Klimisch category 4

References: BIOFAX Industrial Bio-Test Laboratories, Inc. 1971. Data sheets. 19-3. In Registry of Toxic Effects of Chemical Substances. 1999. Sodium acetate. National Institute for Occupational Safety and Health.

### 5.1.3 ACUTE DERMAL TOXICITY

(a)  
 Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LD<sub>L0</sub> [ ]; Other [ ]  
 Species/strain: Rabbit  
 Value: 1060 mg/kg b.w  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid (64-19-7)  
 Reliability: Klimisch category 4  
 References: Union Carbide Corporation. 1963. Union Carbide data sheet. Union Carbide Corporation. Industrial Medicine & Technology. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)  
 Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LD<sub>L0</sub> [ ]; Other [ ]  
 Species/strain: Rabbit  
 Value: > 20,000 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Dose was administered via a single skin penetration to three female albino New Zealand rabbits and kept in place by gauze patches under a latex rubber film.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Fumaric Acid (110-17-8)  
 Remarks: No mortality was observed at the high dose of 20,000 mg/kg b.w.  
 Reliability: Klimisch category 2  
 References: Vernot, E.H., MacEwen, J.D., Haun, C.C., and Kinkead, E.R. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42:417-423.

(c)  
 Type: LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [ ]; LD<sub>L0</sub> [ ]; Other [X]  
 Species/strain: Rabbit  
 Results: 3 minute exposure = very slight erythema (hair on site); no edema  
 24 and 48 hrs after 3 minute exposure = no erythema and no edema  
 60 minute exposure = very slight erythema; no edema

	<p>24 and 48 hrs after 60 minute exposure = no erythema; no edema</p> <p>4hr exposure = very slight-moderate to severe erythema; very slight – moderate edema</p> <p>24 hrs after 4 hr exposure = very slight-moderate to severe erythema; very slight – moderate edema</p> <p>48 hrs after 4 hr exposure = Well defined erythema; slight – no edema</p>
Method:	<p><i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i></p> <p>According to DOT 3-1/10-07-91/REV5 (49 CFR). Young adult, New Zealand White rabbits (five males and three females) were used in this study. The test material was initially applied to one animal for a 3 minute exposure period. Due to the absence of skin corrosion in this initial animal, a second animal was initiated utilizing a 60 minute exposure period. Due to the absence of skin corrosion for the 60 minute exposure period, the test material was ultimately administered to six additional animals for an exposure period of 4 hours. Each animal received on 0.5 ml quantity of undiluted test material each of which was applied in this manner to one intact skin site per animal.</p> <p>Three (3) minute, twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a three minute exposure period.</p> <p>Sixty (60) minute, twenty-four (24), and forty-eight(48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a sixty minute exposure period.</p> <p>Four (4), twenty-four (24), and forty-eight (48) hour skin scores, derived from the intact skin site were evaluated for corrosion in the rabbit receiving a four hour exposure period.</p>
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/>
Test substance:	Citric Acid (77-92-9), purity: 60%
Remarks:	Corrosion was considered to have occurred if the substance in contact with the intact rabbit skin caused destruction or irreversible alteration of the tissue of two or more rabbits. Tissue destruction was considered to have occurred if, at any of the readings, there was ulceration or necrosis. Test generally follows GLP procedures.
Reliability:	Klimisch category 2

References: Hill Top Biolabs, Inc. 1992. D.O.T. corrosivity potential study in rabbits of : Citric acid solution, 60% for Cargill, Inc. Hill Top Biolabs project No. 92-8758-21 (A). Cargill, Inc. Project No. ED76904.

#### 5.1.4 ACUTE TOXICITY BY OTHER ROUTES OF ADMINISTRATION

(e.g. subcutaneous, intravenous, etc.)

(a)  
 Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
 Species/strain: Mouse  
 Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]  
 Value: 525 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid (64-19-7)  
 References: Oro, L. and Wretling, A. 1961. Acta Pharmacol. 18:141. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. Volume II, Part E. Toxicology. New York: John Wiley & Sons, Inc.

(b)  
 Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
 Species/strain: Rat  
 Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]  
 Value: 632 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
 References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(c)  
 Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
 Species/strain: Mouse  
 Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]  
 Value: 98 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated



GLP: Yes ☐ No ☐ ? ☒ [X]  
 Test substance: Acetic Acid, Ammonium Salt (631-61-8)  
 References: Lewis, R.T. (ed.) 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(d)  
 Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ;  
 LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> [X]; LDL<sub>0</sub> ☐ ; Other ☐   
 Species/strain: Mouse  
 Route of Administration: i.m. ☐ ; i.p. ☐ ; i.v. [X]; Infusion ☐ ; s.c. ☐ ; Other ☐   
 Value: 52 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated

GLP: Yes ☐ No ☐ ? ☒ [X]  
 Test substance: Acetic Acid, Calcium Salt (62-54-4)  
 References: Welch et al. 1944. J. Lab. Clin. Med. 29:809. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(e)  
 Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ;  
 LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> [X]; LDL<sub>0</sub> ☐ ; Other ☐   
 Species/strain: Mouse  
 Route of Administration: i.m. ☐ ; i.p. ☐ ; i.v. ☐ ; Infusion ☐ ; s.c. [X]; Other ☐   
 Value: 3,200 mg/kg b.w.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Mice were C3H strain and weighed 25 ± 5g.

GLP: Yes ☐ No [X] ? ☐   
 Test substance: Acetic Acid, Sodium Salt (127-09-3)  
 Reliability: Klimisch category 2  
 References: Allen, H.R., Tucker, R.K., and Geren, C.R. 1986. Potentiation of the toxicity of basic peptides from rattlesnake venoms by acetic acid, sodium salt. *Toxicol* 24(6):553-558.

(f)  
 Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ;  
 LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☐ ; LDL<sub>0</sub> ☐ ; Other [X]  
 Species/strain: Rat  
 Route of Administration: i.m. ☐ ; i.p. [X]; i.v. ☐ ; Infusion ☐ ; s.c. ☐ ; Other ☐   
 Results: 10 mg/kg injected intraperitoneally in rats causes hepatotoxicity, tremors, and hypothermia. 100 mg/kg decreases motor activity and causes diuresis.  
 Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Not stated  
 GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Fumaric Acid (110-17-8)

References: Mileski, D.R., Kaplan, H.R., Malone, M.H., and Nieforth, K.A. 1965. J. Pharm. Sci. 54: 295. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4<sup>th</sup> Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(g)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]

Species/strain: Mouse

Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 200 mg/kg b.w.

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Analyzed using Behren's method which is described in Statistical Methods in Biological Assay. 1952. p.535.

GLP: Yes [ ] No [X] ? [ ]

Test substance: Fumaric Acid (110-17-8)

Remarks: Data as cited in Smith. Data from Upjohn Dept of Pharmacology.

Reliability: Klimisch category 2

References: Smith, C.G., Grady, J.E., and Northam, J.I. 1963. Relationship between cytotoxicity in vitro and whole animal toxicity. Cancer Chemother. Rep. 30:9-12.

(h)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]

Species/strain: Rat

Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 100 mg/kg

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated

GLP: Yes [ ] No [ ] ? [X]

Test substance: Malic Acid (6915-15-7)

References: Eastman Kodak. 1981. Health Safety and Human Factors Laboratory, Rochester, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]

Species/strain: Rat

Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [ ]; Infusion [ ]; s.c. [X]; Other [ ]

Value: 5500 mg/kg

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six 5-week old male SD-JCL rats weighing 110-140 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate

Remarks: Observed effects include respiratory failure and emaciation.

Reliability: Klimisch category 2

References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(j)

Type: LC<sub>0</sub> ☐; LC<sub>100</sub> ☐; LC<sub>50</sub> ☐; LCL<sub>0</sub> ☐; LD<sub>0</sub> ☐; LD<sub>100</sub> ☐; LD<sub>50</sub> ☒; LDL<sub>0</sub> ☐; Other ☐

Species/strain: Mouse

Route of Administration: i.m. ☐; i.p. ☐; i.v. ☐; Infusion ☐; s.c. ☒; Other ☐

Value: 2700 mg/kg

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six 4-week old male ICR-JCL mice weighing 20-24 g were used at each dosage group. A single oral dose was administered for each of a series of concentrations in volumes of 2 ml/100 g body weight. Behavior and mortality were observed for 7 days.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate

Remarks: Observed effects include respiratory failure and emaciation.

Reliability: Klimisch category 2

References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)

Type: LC<sub>0</sub> ☐; LC<sub>100</sub> ☐; LC<sub>50</sub> ☐; LCL<sub>0</sub> ☐; LD<sub>0</sub> ☐; LD<sub>100</sub> ☐; LD<sub>50</sub> ☐; LDL<sub>0</sub> ☐; Other ☒

Species/strain: Horse

Route of Administration: i.m. ☐; i.p. ☐; i.v. ☒; Infusion ☐; s.c. ☐; Other ☐

Results: No significant cardiovascular effects or effects on blood composition in horses injected with 0.56 mg/kg b.w. of citric acid, sodium salt.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six horses were used.

GLP: Yes ☐ No ☐ ? ☒

Test substance: Citric Acid, Sodium Salt (994-36-5)

References: Hubbell, J.A.E., et al. 1987. Vet. Surg. 16:245. In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(l)

Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ; LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Rat

Route of Administration: i.m. ☐ ; i.p. ☒ ; i.v. ☐ ; Infusion ☐ ; s.c. ☐ ; Other ☐

Value: 1,348 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Monosodium citrate (18996-35-5)

References: Journal of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(m)

Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ; LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Mouse

Route of Administration: i.m. ☐ ; i.p. ☒ ; i.v. ☐ ; Infusion ☐ ; s.c. ☐ ; Other ☐

Value: 1,635 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Monosodium citrate (18996-35-5)

References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(n)

Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ; LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐

Species/strain: Dog

Route of Administration: i.m. ☐ ; i.p. ☐ ; i.v. ☒ ; Infusion ☐ ; s.c. ☐ ; Other ☐

Value: 167 mg/kg b.w.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Not stated

GLP: Yes ☐ No ☐ ? ☒

Test substance: Citric Acid, Tripotassium Salt (866-84-2)  
References: American Veterinary Review. 1937. 44:555. In Lewis, R.T. (ed.). 1994. Sax's Dangerous Properties of Industrial Materials. Eighth Edition. New York: Van Nostrand Reinhold Company.

(o)  
Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Rat  
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]  
Value: 1,548 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Citric Acid, Trisodium Salt (64-08-2)  
Remarks: Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.  
Reliability: Klimisch category 4  
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(p)  
Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Mouse  
Route of Administration: i.m. [ ]; i.p. [X]; i.v. [ ]; Infusion [ ]; s.c. [ ]; Other [ ]  
Value: 1,364 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Citric Acid, Trisodium Salt (64-08-2)  
Remarks: Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.  
Reliability: Klimisch category 4  
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(q)  
Type: LC<sub>0</sub> [ ]; LC<sub>100</sub> [ ]; LC<sub>50</sub> [ ]; LCL<sub>0</sub> [ ]; LD<sub>0</sub> [ ]; LD<sub>100</sub> [ ]; LD<sub>50</sub> [X]; LDL<sub>0</sub> [ ]; Other [ ]  
Species/strain: Mouse  
Route of Administration: i.m. [ ]; i.p. [ ]; i.v. [X]; Infusion [ ]; s.c. [ ]; Other [ ]

Value: 170 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Citric Acid, Trisodium Salt (64-08-2)  
Remarks: Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.  
Reliability: Klimisch category 4  
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(r)  
Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ; LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐  
Species/strain: Rabbit  
Route of Administration: i.m. ☐ ; i.p. ☐ ; i.v. ☒ ; Infusion ☐ ; s.c. ☐ ; Other ☐  
Value: 449 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Citric Acid, Trisodium Salt (64-08-2)  
Remarks: Effects noted at the high concentrations included convulsions or effect on seizure threshold; cyanosis; changes in structure or function of salivary glands.  
Reliability: Klimisch category 4  
References: J. of Pharmacol. Exp. Therapeutics. 1948. 94:65. In Registry of Toxic Effects of Chemical Substances. 1999. Trisodium citrate. National Institute for Occupational Safety and Health.

(s)  
Type: LC<sub>0</sub> ☐ ; LC<sub>100</sub> ☐ ; LC<sub>50</sub> ☐ ; LCL<sub>0</sub> ☐ ; LD<sub>0</sub> ☐ ; LD<sub>100</sub> ☐ ; LD<sub>50</sub> ☒ ; LDL<sub>0</sub> ☐ ; Other ☐  
Species/strain: Mouse  
Route of Administration: i.m. ☐ ; i.p. ☐ ; i.v. ☒ ; Infusion ☐ ; s.c. ☐ ; Other ☐  
Value: 111 mg/kg b.w.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Not stated  
GLP: Yes ☐ No ☐ ? ☒  
Test substance: Acetic Acid, Magnesium Salt (142-72-3)  
Reliability: Klimisch category 4  
References: J. Clin. Lab. Med. 1944. 29: 804. In Registry of Toxic Effects of Chemical Substances. 2000. Acetic acid, magnesium salt. National Institute for Occupational Safety and Health.

## 5.4 REPEATED DOSE TOXICITY

(a)	
Species/strain:	Rat
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	oral
Exposure period:	8 months
Frequency of treatment:	3 times per week
Dose:	0.5 ml of 3% water solution of acetic acid (about 60 mg/kg bw/treatment)
Control group:	Yes [ ]; No [X]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	As expected, rats treated with the carcinogen NSEE had high incidences of pre-neoplastic lesions of the esophagus and forestomach, as well as benign tumors, carcinomas and squamous cell cancer. Prolonged administration of acetic acid in combination with NSEE resulted in an increase in the number of benign and malignant tumors and carcinomas in the esophagus. Prolonged administration of acetic acid alone did not induce tumors. All nine of these rats, however, did experience hyperplasia in the esophagus and forestomach.
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> Nine outbred white male rats weighing approximately 100 g were used in the acetic acid alone study. Rats were given either N-nitrosarcosin ethyl ester (NSEE; a known carcinogen) alone, NSEE with the acetic acid solution, or the acetic acid solution alone. All doses were given by intubation into the esophagus. Animals were killed by ether inhalation after 8 months of experiments and autopsied.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic acid (64-17-9)
Reliability:	Klimisch category 2
References:	Alexandrov, V.A., Novikov, A.I., Zabezhinsky, M.A., Stolyarov, V.I., and Petrov, A.S. 1989. The stimulating effect of acetic acid, alcohol, and thermal burn injury on esophagus and forestomach carcinogenesis induced by n-nitrososarcosin ethyl ester in rats. <i>Cancer Lett.</i> 47:79-185.
(b)	
Species/strain:	Rat and mouse
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Inhalation
Exposure period:	3-35 days
Frequency of treatment:	Continuous

Dose: 11-35 ppm  
 Control group: Yes [ ]; No [ ]; No Data [X]  
 Concurrent no treatment [ ]; Concurrent vehicle [ ];  
 Historical [ ]  
 Results: At 15 ppm (for 22 days) or more, the animals showed decreased activity, behavioral changes and reduced work capacity. At 23-31 ppm (17-35 days), there was decreased growth, increased spleen weight, an increase of the level of iron stored in the spleen, signs of kidney damage and increased kidney weights.  
 Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Groups of at least 10 rats and 10 mice were used.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Acetic Acid (64-19-7)  
 Reliability: Klimisch category 2  
 References: Savina, V.P. and Anisimov, B.V. 1987. Kosm. Biol. Aviakosm. Med. 21:79. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(c)  
 Species/strain: Rat (Long-Evans hooded)  
 Sex: Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]  
 Route of Administration: oral (in drinking water)  
 Exposure period: 8 months  
 Frequency of treatment: daily *ad libitum*  
 Dose: 50 and 500 ppm  
 Control group: Yes [ ]; No [X]; No Data [ ]  
 Concurrent no treatment [ ]; Concurrent vehicle [ ];  
 Historical [ ]  
 NOAEL: 500 ppm  
 Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
 Long-Evans hooded rats 21 days old at test initiation were used. The test material was administered *ad libitum* for eight months.  
 GLP: Yes [ ] No [X] ? [ ]  
 Test substance: Acetic Acid, Sodium Salt (127-09-3)  
 Remarks: No significant effects on survival, reinforcement behavior, or body weight gain were observed. The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no separate untreated controls are available for comparison.  
 Reliability: Klimisch category 2  
 References: Cory-Slechta, D.A. 1986. Neurobehav. Toxicol. Teratol. 8:237-244. In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.



(d)

Species/strain: Rat

Sex: Female ☐; Male ☐; Male/Female ☐; No Data [X]

Route of Administration: oral in diet

Exposure period: 4 weeks

Frequency of treatment: daily

Dose: 3.58% of the diet (approx. 3.6 g/kg b.w./day)

Control group: Yes ☐; No ☐; No Data [X]  
Concurrent no treatment ☐; Concurrent vehicle ☐;  
Historical ☐

Results: Growth and survival were normal.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
13 young rats were used.

GLP: Yes ☐ No ☐ ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: Dryden, L.P. and Hartman, A.M. 1971. J. Nutr. 101:589. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(e)

Species/strain: Rat

Sex: Female ☐; Male [X]; Male/Female ☐; No Data ☐

Route of Administration: oral in drinking water

Exposure Period: 112 days, beginning at 31 days of age

Frequency of treatment: Continuous

Dose: 100 ppm

Control group: Yes [X]; No ☐; No Data ☐  
Concurrent no treatment [X]; Concurrent vehicle ☐;  
Historical ☐

Results: No mortality or cognitive impairment was observed.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Eight young adult male Wistar rats were exposed to acetic acid, sodium salt in their drinking water. Training in mazes began on day 112 and lasted until day 157 at which time all animals were sacrificed.

GLP: Yes ☐ No ☐ ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Remarks: The rats treated with acetic acid, sodium salt served as the control for a lead exposure study. Therefore, no untreated controls are available for comparison.

Reliability: Klimisch category 2

References: Massaro, E.J. and Massaro, T.F. 1987. Low level lead exposure during neonatal development perturbs cognitive function. J. Am. Coll. Toxicol. 6(4):441-450.

(f)

Species/strain: Rat

Sex: Female ☐; Male ☐; Male/Female ☐; No Data [X]

Route of Administration: oral in diet

Exposure period: 3 months

Frequency of treatment: daily

Dose: 21 mg/kg b.w./day

Control group: Yes ☐; No ☐; No Data [X]  
Concurrent no treatment ☐; Concurrent vehicle ☐; Historical ☐

Results: Indications of altered thyroid function and decreased growth were reported.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Ten rats were used.

GLP: Yes ☐ No ☐ ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: Goldman, M. 1981. *Experientia* 37:1348. In BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(g)

Species/strain: Rat

Sex: Female ☐; Male ☐; Male/Female [X]; No Data ☐

Route of Administration: oral in diet

Exposure period: 2 years

Frequency of treatment: daily

Dose: female and male rats: 0.1, 0.5, 0.8 or 1.2% fumaric acid  
male rats: 0.5, 1, or 1.5% fumaric acid

Control group: Yes ☐; No ☐; No Data [X]  
Concurrent no treatment ☐; Concurrent vehicle ☐; Historical ☐

Results: Slightly increased mortality and increased incidence of testes degeneration were observed in rats fed 1.5% fumaric acid (approximately 750 mg/kg b.w./day). Two rats receiving 1% or 0.5% had stomach inflammation.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Groups of 12 male and 12 female rats or groups of just male rats were fed the stated doses in the diet.

GLP: Yes ☐ No ☐ ? [X]

Test substance: Fumaric Acid (110-17-8)

Reliability: Klimisch category 2

References: Fitzhugh, O.G. and Nelson, A.A. 1947. *J. Am. Pharm. Assoc.* 36:217. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(h)

Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	Oral
Exposure period:	2 years
Frequency of treatment:	Daily
Dose:	0.05, 0.5 or 5% in diet (equivalent to 2-200 mg/kg bw/day)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [ ]; Concurrent vehicle [ ]; Historical [ ]
Results:	No tissue abnormalities or changes in the blood or urine were observed. Changes in organ weights, and in the first year, decreased growth, and hunched appearance were observed in rats receiving 200 mg/kg bw/day.
Method:	[e.g. OECD, other (with the year of publication or updating of the method used)] Not stated
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Remarks:	The percent in diet is stated to be equivalent to 2-200 mg kg b.w./day, but BIBRA notes that the values in the region of 25-2,500 mg/kg b.w./day seem more likely.
Reliability:	Klimisch category 2
References:	Hazleton Laboratories. 1971. 24-Month dietary administration-rats and 104-week dietary administration-dogs [Material X-5120]. Final reports submitted to Allied Chemical Corporation, Buffalo, New York. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain:	Rabbit
Sex:	Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]
Route of Administration:	oral in diet
Exposure period:	150 days
Frequency of treatment:	daily
Dose:	7.7% citric acid, sodium salt (~5% free acid)
Control group:	Yes [X]; No [ ]; No Data [ ] Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]
Results:	No gross or histopathological changes or difference in growth or survival found.
Method:	[e.g. OECD, other (with the year of publication or updating of the method used)] Rabbits were exposed to citric acid, sodium salt in the diet for 150 days.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 2

References: Packman, E.W., Abbott, D.D., and Harrison, J.W.E. 1963. Toxicol. Appl. Pharmacol. 5:163. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4<sup>th</sup> Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(j)  
Species/strain: Rat (Sprague-Dawley)  
Sex: Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]  
Route of Administration: oral in diet  
Exposure period: 6 weeks  
Frequency of treatment: daily  
Post exposure observation period: none  
Dose: 0.2, 2.4, and 4.8%  
Control group: Yes [X]; No [ ]; No Data [ ]  
Concurrent no treatment [X]; Concurrent vehicle [ ];  
Historical [ ]  
NOEL: 2,260 mg/kg bw  
LOAEL: 4,670 mg/kg bw  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Male SD-JCL rats weighing 98 to 112 g, and 29 to 35 days old at test initiation were fed citric acid in the diet. Four groups of 10 animals each were maintained at 23 ± 1°C for 6 weeks. Body weight was measured in all animals 2 times per week, food intake was measured in a group of five animals twice per week, and any behavioral abnormalities were observed daily.  
GLP: Yes [ ] No [X] ? [ ]  
Test substance: Citric Acid (77-92-9); purity: 99.8% citric acid monohydrate  
Remarks: No behavioral abnormalities, effects on body weight gain, or mortality were observed. Some minor biochemical changes were observed with the highest dose, but no specific pathohistological abnormalities were detected.  
Reliability: Klimisch category 2  
References: Yokotani, H., Usui, T., Nakaguchi, T., Kanabayashi, T. Tanda, M., and Aramaki, Y. 1971. Acute and subacute toxicological studies of TAKEDA-citric acid in mice and rats. J. Takeda Res. lab. 30(1):25-31.

(k)  
Species/strain: Rat  
Sex: Female [ ]; Male [ ]; Male/Female [ ]; No Data [X]  
Route of Administration: oral in diet  
Exposure period: ~ 1 year  
Frequency of treatment: daily  
Dose: 0.1%

Control group: Yes [X]; No [ ]; No Data [ ]  
 Concurrent no treatment [X]; Concurrent vehicle [ ];  
 Historical [ ]  
 Results: No adverse effects were found.  
 Method: [e.g. OECD, other (with the year of publication or  
 updating of the method used)]  
 Two successive generations of rats were fed 0.1% citric  
 acid, sodium salt in the diet.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid, Sodium Salt (994-36-5)  
 Remarks: A limited number of tissues were examined  
 microscopically.  
 Reliability: Klimisch category 2  
 References: Bonting, S.L., and Jansen, B.C.P. 1956. Voeding 17:  
 137. In BIBRA. 1993. Toxicology profile: Citric acid  
 and its common salts. BIBRA International.

(l)  
 Species/strain: Rat  
 Sex: Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]  
 Route of Administration: oral in diet  
 Exposure period: 32 weeks  
 Frequency of treatment: daily  
 Dose: 5% (~2,500 mg/kg b.w./day)  
 Control group: Yes [X]; No [ ]; No Data [ ]  
 Concurrent no treatment [X]; Concurrent vehicle [ ];  
 Historical [ ]  
 Results: No overt signs of toxicity were observed.  
 Method: [e.g. OECD, other (with the year of publication or  
 updating of the method used)]  
 Twenty male rats were fed 5% citric acid, sodium salt in  
 the diet for 32 weeks (about 2,500 mg/kg b.w./day).  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid, Sodium Salt (994-36-5)  
 Reliability: Klimisch category 2  
 References: Fukushima, S., et al. 1986. Gann 77:1. In BIBRA.  
 1993. Toxicology profile: Citric acid and its common  
 salts. BIBRA International

(m)  
 Species/strain: Mouse  
 Sex: Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]  
 Route of Administration: oral feed  
 Exposure period: 12 months  
 Frequency of treatment: Continuous in the diet  
 Post exposure observation period: None  
 Dose: 2 g Mn/kg of food in the form of acetic acid, manganese  
 salt  
 Control group: Yes [X]; No [ ]; No Data [ ]  
 Concurrent no treatment [X]; Concurrent vehicle [ ];  
 Historical [ ]

Results: No mortality was observed during the experiment. By the end of the study, body weight gain was significantly suppressed in the treatment mice compared to the controls ( $P < 0.05$ ). When body weight gain became less than that of the control, changes in spontaneous motor activity were noted. In the hypothalamus, dopamine levels decreased significantly ( $P < 0.05$ ) and the manganese content increased up to 13 times compared to the controls.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Six-week old male ddY mice weighing  $29.1 \pm 0.2$  g were divided into two groups with six mice in each. The first group served as the control and the second received 2 g Mn/kg in the form of acetic acid, manganese salt in the diet for twelve months. All animals were allowed free access to food and water. Body weight changes were recorded and spontaneous motor activity was tested. Urine, blood, and tissue samples were analyzed. Mice were decapitated 24 hours after last feeding.

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid, Manganese Salt (638-38-0)

Reliability: Klimisch category 2

References: Komura, J. and Sakamoto, M. 1992. Effects of manganese forms on biogenic amines in the brain and behavioral alterations in the mouse: Long-term oral administration of several manganese compounds. Environ. Res. 57(1):34-44.

## 5.5 GENETIC TOXICITY *IN VITRO*

### A. Bacterial Test

(a)

Type: Bacterial reverse mutation assay

System of testing: TA 98, TA 100, TA 1535, TA 1537, and TA 1538

Metabolic activation: With ☐; Without ☐; With and Without ☒ [X];  
No Data ☐ [ ]

Results:

Genotoxic effects:		+	?	-
	With metabolic activation:	<input type="checkbox"/> [ ]	<input type="checkbox"/> [ ]	<input checked="" type="checkbox"/> [X]
	Without metabolic activation:	<input type="checkbox"/> [ ]	<input type="checkbox"/> [ ]	<input checked="" type="checkbox"/> [X]

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Ames test

GLP: Yes ☐ No ☐ ? ☒ [X]

Test substance: Acetic Acid (64-19-7)

Reliability: Klimisch category 2

References: NcMahon et al. 1979. Cancer Res. 39:682-693. In European Commission. 1996. Acetic acid. International Uniform Chemical Information Database.

(b)

Type: Bacterial reverse mutation assay

System of testing: *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 97 and/or TA 1537.

Concentration: 100, 333, 1000, 3333, 6666, 10000 µg/plate

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results:

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Standard Ames test.

GLP: Yes [X] No [ ] ? [ ]

Test substance: Acetic Acid (64-19-7), purity: 99%

Remarks: Tested within the National Toxicology Program's mutagenicity testing program.

Reliability: Klimisch category 1

References: Zeiger, E., Anderson, B., Haworth, S. Lawlor, T., and Mortelmans, K. 1992. Salmonella mutagenicity test: V. results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19(Suppl. 21):2-141.

(c)

Type: Bacterial reverse mutation assay

Metabolic activation: With [ ]; Without [ ]; With and Without [X]; No Data [ ]

Results: Acetic acid and its sodium and zinc salts have given no evidence of mutagenic activity in good-quality Ames tests using *Salmonella typhimurium* either with or without S9.

Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Ames test

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid (64-19-7); Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: BIBRA. 1993. Toxicology profile: Acetic acid and its common salts. BIBRA International.

(d)

Type: Bacterial reverse mutation assay  
System of testing: *Salmonella typhimurium* strains TA 92, TA 94, TA 98, TA 100, TA 1535, and TA 1537,  
Concentration: maximum concentration of 40 mg/plate  
Metabolic activation: With [X]; Without [ ]; With and Without [ ];  
No Data [ ]  
Results:  
Genotoxic effects: + ? -  
With metabolic activation: [ ] [ ] [X]  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
An Ames test was conducted using the test substance in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Sodium Salt (127-09-3)  
Reliability: Klimisch category 2  
References: Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Fd. Chem. Toxic.* 22(8):623-636.

(e)

Type: Bacterial reverse mutation assay  
System of testing: *Salmonella typhimurium* strains TA 98, TA100, TA 1535, TA 97 and/or TA1537  
Concentration: Not stated  
Metabolic activation: With [ ]; Without [ ]; With and Without [X];  
No Data [ ]  
Results:  
Genotoxic effects: + ? -  
With metabolic activation: [ ] [ ] [X]  
Without metabolic activation: [ ] [ ] [X]  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Ames test.  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Fumaric Acid (110-17-8)  
Reliability: Klimisch category 2  
References: Zeiger, E., et al. 1988. *Environ. Molec. Mutagen.* 11:1. In BIBRA. 1991. Toxicology profile: Fumaric acid and its common salts. BIBRA International.

(f)

Type: Bacterial reverse mutation assay  
System of testing: *Salmonella typhimurium* strain TA 100  
Concentration: 1000, 100, 10, 1, and 0.1 µg/plate  
Metabolic activation: With [ ]; Without [X]; With and Without [ ];  
No Data [ ]



Genotoxic effects:

	+	?	-
Without metabolic activation:	[ ]	[ ]	[X]

[e.g. OECD, other (with the year of publication or updating of the method used)]  
An Ames test was conducted using a constant volume of 0.4 ml of fumaric acid at concentrations of 1000, 100, 10, 1, and 0.1 µg/plate.

Yes [ ] No [ ] ? [X]

Fumaric Acid (110-17-8)  
Klimisch category 2

Rapson, W.H., Nazar, M.A., and Butsky, V.V. 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull. Environm. Toxicol. 24:590-596.

Type:

System of testing:

Concentration:

Metabolic activation:

Results:

Genotoxic effects:

**Method:**

GLP:

Test substance:

### Reliability:

References:

(h)

Type:

System of testing:

Concentration:

Metabolic activation:

Results:

Genotoxic effects:

Bacterial reverse mutation assay  
*Salmonella typhimurium* strains TA 97, TA 98, TA 100,  
and TA 104

0, 1100, 1500, and 2000 µg/plate  
With [ ]; Without [ ]; With and Without [X];  
No Data [ ]

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

[e.g. OECD, other (with the year of publication or updating of the method used)]  
Ames Salmonella/microsome test. All tests were done in triplicate both with and without S9 activation.

Yes [ ] No [ ] ? [X]  
Malic Acid (6915-15-7)

Klimisch category 2

Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the ames salmonella/microsome test. *Mutat. Res.* 206:467-470.

Bacterial reverse mutation assay  
*Salmonella typhimurium* strains TA 97, TA 98, TA 100,  
and TA 104

0, 500, 1000, and 2000 µg/plate  
With [ ]; Without [ ]; With and Without [X]

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Ames *Salmonella*/microsome test. All tests were done in triplicate both with and without S9.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid (77-92-9)  
 Reliability: Klimisch category 2  
 References: Al-Ani, F.Y. and Al-Lami, S.K. 1988. Absence of mutagenic activity of acidity regulators in the Ames *Salmonella*/microsome test. *Mutat. Res.* 206:467-470.

(i)  
 Type: Cytogenetic assay  
 System of testing: *S. cerevisiae* cells  
 Metabolic activation: With [ ]; Without [ ]; With and Without [X];  
 No Data [ ]

Results:  
 Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]
Without metabolic activation:	[ ]	[ ]	[X]

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 Ames test  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Citric Acid, Sodium Salt (994-36-5); Citric Acid, Tripotassium Salt (866-84-2)  
 Reliability: Klimisch category 2  
 References: Litton Bionetics Inc. 1975. Contract No. 223-74-2104 and FDA 71-268. In BIBRA. 1993. Toxicology Profile: Citric acid and its common salts. BIBRA International.

(j)  
 Type: Bacterial reverse mutation assay  
 System of testing: *Salmonella typhimurium* strains TA 92, TA 1535, TA 100, TA 1537, TA 94, and TA 98.  
 Concentration: maximum dose of 5.0 mg/plate  
 Metabolic activation: With [X]; Without [ ]; With and Without [ ];  
 No Data [ ]

Results:  
 Genotoxic effects:

	+	?	-
With metabolic activation:	[ ]	[ ]	[X]

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
 An Ames test was conducted using monosodium citrate (18996-35-5) in a phosphate buffer. Six concentrations were tested. Two plates were used for each concentration.  
 GLP: Yes [ ] No [ ] ? [X]  
 Test substance: Monosodium citrate (18996-35-5), purity: 99.6%  
 Reliability: Klimisch category 2

References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. <i>Fd. Chem. Toxic.</i> 22(8):623-636.
(k)	
Type:	Bacterial gene mutation (Rec-assay)
System of testing:	<i>Bacillus subtilis</i> strains H17 (Rec <sup>+</sup> , arg <sup>-</sup> , and trp <sup>-</sup> ) and M45 (Rec <sup>+</sup> , arg <sup>-</sup> , and trp <sup>-</sup> )
Concentration:	0.05 M
Results:	< 5 mm distance (weakly positive)
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> Each assay was repeated three times. An 0.05 aliquot of acetic acid, manganese salt (0.05 M) was dropped onto a 10 mm diameter filter paper disk. Plates were incubated at 37°C for 24 hours. The inhibition of growth is indicated by the distance (mm) between the edge of a paper disc and that of streaks. The difference between the inhibition zones for Rec <sup>+</sup> and Rec <sup>-</sup> cells may be due to cellular repair. This is called “rec-effect”.
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/> [X]
Test substance:	Acetic Acid, Manganese Salt (638-38-0),
Reliability:	Klimisch category 2
References:	Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. <i>Mutat. Res.</i> 31:185-189.

## B. Non-bacterial *in vitro* test

(a)	
Type:	Cytogenetic assay
Concentration:	≤16 mM
System of testing:	Chinese hamster ovary K1 cells
Results:	Acetic acid was not clastogenic at concentrations close to those showing cytotoxicity.
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> CHO test guideline
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/> [X]
Test substance:	Acetic Acid (64-19-7)
Remarks:	Low pH did induce some artificial chromosome aberrations, but these were eliminated by neutralization of the test medium.
Reliability:	Klimisch category 2
References:	Morita, T. Takeda, K., and Okumura, K. 1990. <i>Mutat. Res.</i> 240:195. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. <u>Patty's Industrial Hygiene and Toxicology</u> . 4 <sup>th</sup> Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(b)

Type: Cytogenetic assay  
System of testing: Chinese hamster fibroblast cell line  
Concentration: maximum dose of 1 mg/ml  
Metabolic activation: With [ ]; Without [X]; With and Without [ ];  
No Data [ ]  
Results:  
Genotoxic effects: + ? -  
Without metabolic activation: [ ] [ ] [X]  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Substance was tested in a physiological saline solvent.  
Three different concentrations were tested and cells were exposed to each concentration for 48 hours.  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Acetic Acid, Sodium Salt (127-09-3)  
Reliability: Klimisch category 2  
References: Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Fd. Chem. Toxic.* 22(8):623-636.

(c)

Type: Cytogenetic assay  
System of testing: Chinese hamster fibroblast cell line  
Concentration: maximum dose of 0.5 mg/ml  
Metabolic activation: With [ ]; Without [X]; With and Without [ ];  
No Data [ ]  
Results:  
Genotoxic effects: + ? -  
Without metabolic activation: [ ] [ ] [X]  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Substance was tested in a physiological saline solvent.  
Three different concentrations were tested and cells were exposed to each concentration for 24 hours.  
GLP: Yes [ ] No [ ] ? [X]  
Test substance: Fumaric Acid (110-17-8), purity: 99.7%  
Reliability: Klimisch category 2  
References: Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Fd. Chem. Toxic.* 22(8):623-636.

(d)

Type: Cytogenetic assay  
System of testing: Chinese hamster fibroblast cell line  
Concentration: maximum dose of 1 mg/ml

Metabolic activation:	With [ ]; Without [X]; With and Without [ ]; No Data [ ]
Results:	
Genotoxic effects:	<div style="text-align: right; margin-right: 20px;"> +           ?           - </div> Without metabolic activation: [ ]   [ ]   [X]
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> Substance was tested in a physiological saline solvent. Three different concentrations were tested and cells were exposed to each concentration for 48 hours.
GLP:	Yes [ ] No [ ] ? [X]
Test substance:	Malic Acid (6915-15-7)
Reliability:	Klimisch category 2
References:	Ishidate, M., Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T. Sawada, M., and Matsouka, A. 1984. Primary mutagenicity screening of food additives currently used in Japan. <i>Fd. Chem. Toxic.</i> 22(8):623-636.

## 5.6 GENETIC TOXICITY *IN VIVO*

(a)	
Type:	Testicular DNA-synthesis inhibition test
Species/strain:	Mouse
Sex:	Female [ ]; Male [X]; Male/Female [ ]; No Data [ ]
Route of Administration:	gavage
Exposure period:	single application
Doses:	200, 500, and 1,000 mg/kg
Results:	No inhibitory effect on DNA-replication was detectable.
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> 3H-thymidine incorporation was measured.
GLP:	Yes [ ] No [X] ? [ ]
Test substance:	Acetic Acid, Sodium Salt (127-09-3)
Remarks:	This is not a standard genotoxicity test system, but it provides evidence that acetic acid, sodium salt is not genotoxic in animals.
Reliability:	Klimisch category 2
References:	Seiler, J.P. 1981. The testicular DNA-synthesis inhibition test (DSI Test). In <i>Short Tests Chem Carcinogen</i> . In European Commission. 1996. Sodium acetate. International Uniform Chemical Information Database.
(b)	
Type:	Dominant lethal assay
Species/strain:	Rat
Sex:	Female [ ]; Male [ ]; Male/Female [X]; No Data [ ]
Route of Administration:	Not stated
Exposure period:	5 days

Doses:	3 g/kg
Results:	No mutagenic potential was detected.
Method:	[e.g. OECD, other (with the year of publication or updating of the method used)]
	Not stated
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/> [X]
Test substance:	Citric Acid (77-92-9)
Reliability:	Klimisch category 4
References:	Litton Bionetics, Inc. 1975. Contract No. FDA 71-268. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

## 5.8 TOXICITY TO REPRODUCTION

(a)

Type:	Fertility <input type="checkbox"/> ; One-generation study <input checked="" type="checkbox"/> [X]; Two-generation study <input type="checkbox"/> ; Other <input type="checkbox"/>
Species/strain:	Guinea pig
Sex:	Female <input type="checkbox"/> ; Male <input type="checkbox"/> ; Male/Female <input checked="" type="checkbox"/> [X]; No Data <input type="checkbox"/>
Route of Administration:	oral in feed
Frequency of treatment:	daily
Doses:	1% (~ 400 mg/kg b.w./ day)
Control group:	Yes <input type="checkbox"/> ; No <input checked="" type="checkbox"/> [X]; No Data <input type="checkbox"/> Concurrent no treatment <input type="checkbox"/> ; Concurrent vehicle <input type="checkbox"/> ; Historical <input type="checkbox"/>
NOEL Parental:	400 mg/kg bw/ day
NOEL F1 Offspring:	400 mg/kg bw/ day
Results:	There were no detectable toxic effects on growth, reproduction or lactation.
Method:	[e.g. OECD, other (with the year of publication or updating of the method used)] Two pregnant females received fumaric acid in their diet. Combined, they produced 12 offspring. The males were also fed fumaric acid in the diet.
GLP:	Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> [X] ? <input type="checkbox"/>
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 4
References:	Levey, S. et al. 1946. J. Am. Pharm. Assoc. 35:298. In European Commission. 1996. Fumaric acid. International Uniform Chemical Information Database.

(b)

Type:	Fertility <input checked="" type="checkbox"/> [X]; One-generation study <input type="checkbox"/> ; Two-generation study <input type="checkbox"/> ; Other <input type="checkbox"/>
Species/strain:	Rat
Sex:	Female <input checked="" type="checkbox"/> [X]; Male <input type="checkbox"/> ; Male/Female <input type="checkbox"/> ; No Data <input type="checkbox"/>
Route of Administration:	oral in diet
Exposure period:	several months
Frequency of treatment:	daily
Doses:	600 mg/kg b.w

Control group: Yes ☐ ; No ☐ ; No Data [X]  
Concurrent no treatment ☐ ; Concurrent vehicle ☐ ;  
Historical ☐

NOAEL: = 600 mg/kg bw  
LOAEL: >600 mg/kg bw  
Results: No reproductive effects detected.  
Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Rats were fed diets containing 1.2% citric acid (about 600 mg/kg bw/ day). Exposure began 29 weeks prior to mating and continued for a few months after mating.

GLP: Yes ☐ No ☐ ? [X]  
Test substance: Citric Acid (77-92-9)  
Reliability: Klimisch category 2  
References: Bonting and Jansen. 1956. Voeding 17:137. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database. Also, In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

(c)

Type: Fertility [X]; One-generation study [X]; Two-generation study ☐ ; Other ☐

Species/strain: Rat and mouse  
Sex: Female [X]; Male ☐ ; Male/Female ☐ ; No Data ☐

Route of Administration: oral in diet  
Frequency of treatment: daily  
Doses: 5%  
Control group: Yes ☐ ; No ☐ ; No Data [X]  
Concurrent no treatment ☐ ; Concurrent vehicle ☐ ;  
Historical ☐

Results: No effects on reproduction, litter size or survival up to weaning were detected. A decrease in body weight gain and reduced survival time in mice were observed.

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]  
Female rats and mice were fed diets containing 5% citric acid (about 2.5 g/kg bw/day) before, during, and after mating.

GLP: Yes ☐ No ☐ ? [X]  
Test substance: Citric Acid (77-92-9)  
Remarks: The effects on body weight gain and survival time may have resulted from the chelating ability of citric acid, which could impair absorption of calcium and iron.

Reliability: Klimisch category 2  
References: Wright, E. and Hughes, R.E. 1976. Nutr. Rep. Int. 13:563. In Clayton, G.D. and Clayton, F.E. (eds.). 1994. Patty's Industrial Hygiene and Toxicology. 4<sup>th</sup> Ed. Volume II, Part E: Toxicology. John Wiley & Sons, Inc.

(d)

Type: Fertility [X]; One-generation study [ ]; Two-generation study [ ]; Other [ ]

Species/strain: Rat

Sex: Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]

Route of Administration: oral in diet

Exposure period: several months

Frequency of treatment: daily

Doses: 0.1% citric acid, sodium salt

Control group: Yes [ ]; No [ ]; No Data [X]  
Concurrent no treatment [ ]; Concurrent vehicle [ ];  
Historical [ ]

NOAEL: 0.1% citric acid, sodium salt

LOAEL: >0.1% citric acid, sodium salt

Results: No reproductive effects detected at 0.1% citric acid, sodium salt.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Rats were fed diets containing 0.1% citric acid, sodium salt. Exposure began 29 weeks prior to mating and continued for a few months after mating.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Citric Acid, Sodium Salt (994-36-5)

Reliability: Klimisch category 2

References: Bonting and Jansen. 1956. Voeding 17:137.  
In BIBRA. 1993. Toxicology profile: Citric acid and its common salts. BIBRA International.

## 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a)

Species/strain: Mouse

Sex: Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]

Route of Administration: oral

Duration of the test: 17 days

Exposure period: 10 days

Frequency of treatment: daily

Doses: 0, 16, 74, 345, and 1600 mg/kg bw/day

Control group: Yes [X]; No [ ]; No Data [ ]  
Concurrent no treatment [X]; Concurrent vehicle [ ];  
Historical [ ]

Results: No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Following mating, adult female albino CD-1 mice were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded for 10 days. On day 17, Caesarian sections were performed on all dams and the numbers of



implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Acetic Acid (64-19-7)

Reliability: Klimisch category 2

References: Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(b)

Species/strain: Rat

Sex: Female ☒; Male ☐; Male/Female ☐; No Data ☐

Route of Administration: oral

Duration of the test: 14 days

Exposure period: 10 days

Frequency of treatment: daily

Doses: 0, 16, 74, 345, and 1600 mg/kg bw/day

Control group: Yes ☒; No ☐; No Data ☐

Concurrent no treatment ☒; Concurrent vehicle ☐; Historical ☐

Results: No effects on nidation or on maternal or fetal survival at doses up to 1600 mg/kg bw/day

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*

Following mating, adult female albino rats (Wistar) were dosed daily by oral intubation beginning on day 6 of gestation. Animals were observed daily and body weights recorded. On day 20, Caesarian sections were performed on all dams and the numbers of implantation sites, resorption sites, and live and dead fetuses was recorded. General external and internal examinations were also made of the dams.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Acetic Acid (64-19-7)

Reliability: Klimisch category 2

References: Food and Drug Research Laboratories. 1974. Teratologic Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic Acid; Table Strength 5%) in Mice, Rats and Rabbits. NTIS PB234869.

(c)

Species/strain: Rabbit

Sex: Female ☒; Male ☐; Male/Female ☐; No Data ☐

Route of Administration: oral

Duration of the test: 23 days

Exposure period: 13 days

Frequency of treatment: daily

Doses: 0, 16, 74, 345, and 1600 mg/kg bw/day

Control group: Yes [X]; No [ ]; No Data [ ]  
 Concurrent no treatment [X]; Concurrent vehicle [ ];  
 Historical [ ]

Results: No effects on nidation or on maternal or fetal survival at  
 doses up to 1600 mg/kg bw/day

Method: *[e.g. OECD, other (with the year of publication or  
 updating of the method used)]*  
 Following artificial insemination, adult Dutch-belted  
 female rabbits were dosed daily by oral intubation  
 beginning on day 6 of gestation. Animals were observed  
 daily and body weights recorded. On day 29, Caesarian  
 sections were performed on all does and the numbers of  
 corpora lutea, implantation sites, resorption sites, and  
 live and dead fetuses was recorded. General external  
 and internal examinations were also made of the does.

GLP: Yes [ ] No [X] ? [ ]

Test substance: Acetic Acid (64-19-7)

Reliability: Klimisch category 2

References: Food and Drug Research Laboratories. 1974. Teratologic  
 Evaluation of FDA 71-78 (Apple Cider Vinegar; Acetic  
 Acid; Table Strength 5%) in Mice, Rats and Rabbits.  
 NTIS PB234869.

(d)

Species/strain: Mouse

Sex: Female [X]; Male [ ]; Male/Female [ ]; No Data [ ]

Route of Administration: oral

Exposure period: 5 days (days 8-12 of gestation)

Frequency of treatment: daily

Post exposure observation period: ~ 2weeks

Duration of the test ~ 3 weeks

Doses: 1,000 mg/kg b.w.

Control group: Yes [X]; No [ ]; No Data [ ]  
 Concurrent no treatment [ ]; Concurrent vehicle [X];  
 Historical [ ]

NOEL Parental: 1,000 mg/ kg b.w.

NOEL F1 Offspring: 1,000 mg/kg b.w.

Results: General parental toxicity: No effects  
 Toxicity to offspring: No effects

Method: *[e.g. OECD, other (with the year of publication or  
 updating of the method used)]*  
 30 pregnant CD-1 mice, approximately 60 days old,  
 were give a single oral dose by gavage on days 8-12 of  
 gestation. Animal quarters were maintained at a  
 temperature of 22 °C, a relative humidity of 40-60%,  
 and a 7 am to 7 pm photoperiod.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Reliability: Klimisch category 2

References: Kavlock, R.J., Short, R.D., Jr., and Chernoff, N. 1987. Further evaluation of an *in vivo* teratology screen. Teratog. Carcinog. Mutagen. 7:7-16.

(e)

Species/strain: Fertile single-comb white leghorn chicken eggs

Route of Administration: injection into egg

Frequency of treatment: single injection

Doses: maximum 10.0 mg/egg

Control group: Yes [X]; No [ ]; No Data [ ]

Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]

LD<sub>50</sub>: 4.58 mg/egg

NOAEL teratogenicity: 10.0 mg/egg

Results: No teratogenic response under any of the four test conditions was observed at the highest concentration injected.

Method: [e.g. OECD, other (with the year of publication or updating of the method used)]

Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Sodium Salt (127-09-3)

Remarks: The LD<sub>50</sub> is for the test condition in which the injection was made to the yolk sac at 0 hrs.

Reliability: Klimisch category 3 (non-standard test organism)

References: Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol Appl. Pharmacol. 56:265-273.

(f)

Type: *Drosophila* embryonic cell culture test

Species/strain: *Drosophila* (fruit fly)/Oregon R., Canton S<sub>109</sub>, and Canton S

Doses: 10<sup>-3</sup> M

Control group: Yes [X]; No [ ]; No Data [ ]

Concurrent no treatment [X]; Concurrent vehicle [ ]; Historical [ ]

Results: The *in vitro* assay for fumaric acid was negative. There was no apparent teratogenic effect.

Method:	<p>[e.g. OECD, other (with the year of publication or updating of the method used)]</p> <p><i>Drosophila</i> eggs were homogenized and the embryonic cells were plated out in cell culture dishes at <math>8 \times 10^5</math> cells per ml of medium. After allowing time (15-20 min.) for cells to attach to the bottom of the dish, the medium covering the cells was replaced with medium in which the test substance had been dissolved. Embryonic cells were treated with an initial dose of 0.01 of the LD<sub>50</sub> for adult female <i>Drosophila</i>. Cell and tissue differentiation was scored by counting the number of myotubes and neuron clusters (ganglia). An interference in normal cell differentiation (reduction in the number of myotubes and ganglia compared to the controls), was taken to be an indication of teratogenic response. A total of four dishes per trial were scored. The chemical was tested on three or more separate trials. A 50% reduction in the number of either myotubes and/or ganglia is taken as a teratogenic response.</p>
GLP:	Yes <input type="checkbox"/> No <input type="checkbox"/> ? <input checked="" type="checkbox"/>
Test substance:	Fumaric Acid (110-17-8)
Reliability:	Klimisch category 3 (non-standard study)
References:	Bournias-Vardiabasis, N. Teplitz, R.L., Chernoff, G.F., and Seecof, R., L. 1983. Detection of teratogens in the <i>Drosophila</i> embryonic culture test: Assay of 100 chemicals. <i>Teratology</i> 28:109-122.
(g)	
Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes <input checked="" type="checkbox"/> ; No <input type="checkbox"/> ; No Data <input type="checkbox"/> Concurrent no treatment <input checked="" type="checkbox"/> ; Concurrent vehicle <input checked="" type="checkbox"/> ; Historical <input type="checkbox"/>
LD <sub>50</sub> :	0.42 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	<p>[e.g. OECD, other (with the year of publication or updating of the method used)]</p> <p>Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable</p>

embryos were removed. Surviving embryos were allowed to hatch.

GLP: Yes ☐ No ☐ ? ☒

Test substance: Malic Acid (6915-15-7)

Remarks: The LD<sub>50</sub> for the test condition in which the injection was made to the air sac at 96 hrs.

Reliability: Klimisch category 3 (non-standard study)

References: Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. *Toxicol Appl. Pharmacol.* 56:265-273.

(h)

Type: Fertility ☐; One-generation study ☒; Two-generation study ☐; Other ☐

Species/strain: Rat and mouse

Sex: Female ☒; Male ☐; Male/Female ☐; No Data ☐

Route of Administration: oral

Exposure period: 10 days (days 6-15 of pregnancy)

Frequency of treatment: daily

Doses: Rat: 350 mg/kg b.w.  
Mouse: 266 mg/kg b.w.

Control group: Yes ☒; No ☐; No Data ☐  
Concurrent no treatment ☒; Concurrent vehicle ☐; Historical ☐

NOEL Parental: Rat: 350 mg/kg b.w/day  
Mouse: 266 mg/kg b.w/day

Results: No treatment-related fetal or maternal toxic effects or increases in fetal malformations were observed.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*  
Pregnant rats and mice were given DL-malic acid by stomach tube at doses up to 350 and 266 mg/kg bw/ day, respectively, on days 6-15 of pregnancy.

GLP: Yes ☐ No ☒ ? ☐

Test substance: Malic Acid (6915-15-7)

Reliability: Klimisch category 2

References: Food and Drug Research Laboratories Inc. 1974. Teratologic evaluations of FDA 71-90 in mice and rats. Contract No. FDA 71-260. In BIBRA. 1992. Toxicology profile: Malic acid and its common salts. BIBRA International.

(i)

Species/strain: Rat

Sex: Female ☒; Male ☐; Male/Female ☐; No Data ☐

Route of Administration: oral

Duration of the test: 10 days

Exposure period: days 6-15 of gestation

Frequency of treatment: daily

Doses:	241 mg/kg b.w./day
Control group:	Yes [ <input type="checkbox"/> ]; No [ <input type="checkbox"/> ]; No Data [X] Concurrent no treatment [ <input type="checkbox"/> ]; Concurrent vehicle [ <input type="checkbox"/> ]; Historical [ <input type="checkbox"/> ]
Results:	No indication of adverse effects on nidation (fertilization), maternal, or fetal survival.
NOAEL Maternal:	241 mg/kg b.w.
NOAEL Teratogenicity:	241 mg/kg b.w.
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> Not stated
GLP:	Yes [ <input type="checkbox"/> ] No [ <input type="checkbox"/> ] ? [X]
Test substance:	Citric Acid (77-92-9)
Remarks:	No further data provided in reference.
Reliability:	Klimisch category 2
References:	Food & Drugs Research Laboratories, Inc. 1973. Teratologic evaluation of FDA 71-54. Contract No. 71- 260. In European Commission. 1996. Citric acid. International Uniform Chemical Information Database.

(j)

Species/strain:	Fertile single-comb white leghorn chicken eggs
Route of Administration:	injection into egg
Frequency of treatment:	single injection
Doses:	maximum 10.0 mg/egg
Control group:	Yes [X]; No [ <input type="checkbox"/> ]; No Data [ <input type="checkbox"/> ] Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ <input type="checkbox"/> ]
LD <sub>50</sub> :	2.06 mg/egg
NOAEL teratogenicity:	10.0 mg/egg
Results:	No teratogenic response under any of the four test conditions was observed at the highest concentration injected.
Method:	<i>[e.g. OECD, other (with the year of publication or updating of the method used)]</i> Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.
GLP:	Yes [ <input type="checkbox"/> ] No [ <input type="checkbox"/> ] ? [X]
Test substance:	Citric Acid, Sodium Salt (994-36-5)
Remarks:	The LD <sub>50</sub> is for the test condition in which the injection was made into the air sac at 96 hrs.
Reliability:	Klimisch category 3 (non-standard study)

References: Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. *Toxicol Appl. Pharmacol.* 56:265-273.

(k)

Species/strain: Fertile single-comb white leghorn chicken eggs

Route of Administration: injection into egg

Frequency of treatment: single injection

Doses: maximum 10.0 mg/egg

Control group: Yes [X]; No [ ]; No Data [ ]

Concurrent no treatment [X]; Concurrent vehicle [X]; Historical [ ]

LD<sub>50</sub> (Air cell; 0 hrs): >10.0 mg/egg

LD<sub>50</sub>(Air cell, 96 hrs): 1.47 mg/egg

LD<sub>50</sub>(Yolk sac, 0 hrs): >10.0 mg/egg

LD<sub>50</sub>(Yolk sac, 96 hrs): Estimated to be 12.09 mg/egg by extrapolation on the regression line.

Results: Air cell treatment at preincubation resulted in a high incidence of birds with hypopigmentation of the down. Air cell treatment on the fourth day resulted in a high incidence of birds with severe abnormalities at all 3 test levels that allowed some to hatch. The defects involved primarily the beak, eyes, and eyelids.

Method: *[e.g. OECD, other (with the year of publication or updating of the method used)]*

Fertile eggs from single-comb white leghorn chickens were used. The test substance in water was administered by two routes, injection via the yolk and via the air cell. For each injection route, eggs were treated at two stages of incubation: preincubation (0 hrs) and on the fourth day (96 hrs). At least 100 embryos per each of four dose levels were treated. After treatment, all eggs were candled daily and nonviable embryos were removed. Surviving embryos were allowed to hatch.

GLP: Yes [ ] No [ ] ? [X]

Test substance: Acetic Acid, Manganese Salt (638-38-0)

Remarks: The author considers the hypopigmentation of down to be a toxic effect rather than a teratogenic one.

Reliability: Klimisch category 3 (non-standard study)

References: Verrett, M.J., Scott, W.F., Reynaldo, E.F., Alterman, E.K., and Thomas, C.A. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. *Toxicol Appl. Pharmacol.* 56:265-273.

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